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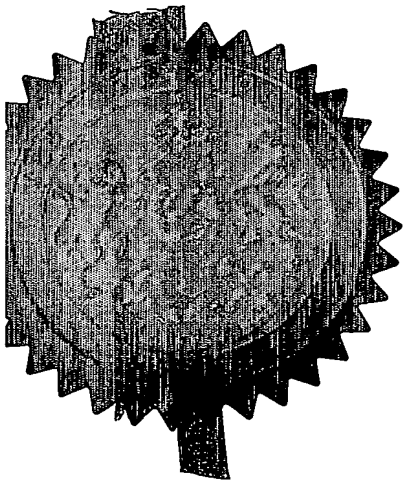

**PRIORITY DOCUMENT**
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Signed Stephen Hordley.

Dated 22 August 2003

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**Patents Form 1/77**

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**The Patent Office**

1/77

## Request for grant of a patent

*(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)*

**The Patent Office**

Cardiff Road
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| | | |
|---|---|---|
| 1. | Your Reference | SAL/PG4798 |
| 2. | Patent application number *(The Patent office will fill in this part)* | 0214149.7 — 19 JUN 2002 |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | ~~GLAXO GROUP LIMITED~~<br>~~GLAXO WELLCOME HOUSE~~<br>~~BERKELEY AVENUE~~<br>~~GREENFORD~~ SMITHKLINE BEECHAM CORPORATION<br>~~MIDDLESEX~~ PO BOX 7929<br>~~UB6 ONN~~ ONE FRANKLIN PLAZA<br>~~GB~~ PHILADELPHIA<br>PENNSYLVANIA 19101<br>~~GB~~ USA |
| | Patents ADP number *(if you know it)* | 05949417004 |
| | If the applicant is a corporate body, give the country/state of its corporation | PENNSYLVANIA |
| 4 | Title of the invention | CHEMICAL COMPOUNDS |
| 5. | Name of your agent *(if you know one)* | STEPHANIE A. LEAROYD |
| | "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | GLAXOSMITHKLINE<br>CORPORATE INTELLECTUAL PROPERTY<br>980 GREAT WEST ROAD<br>BRENTFORD, MIDDLESEX<br>TW8 9GS, GB |
| | Patents ADP number *(if you know it)* | 8082091002 |

| 6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number | Country | Priority application number *(if you know it)* | Date of Filing (day / month / year) |
|---|---|---|---|
| | | | |

| 7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | Number of earlier application | Date of filing (day / month / year) |
|---|---|---|
| | | |

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*
*See note (d))*

YES

9. Enter the number of sheets for any of the

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following items you are filing with th[illegible]m.
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| | |
|---|---|
| Description | 63 |
| Claim(s) | 1 |
| Abstract | 1 |
| Drawing(s) | - |

10. If you are also filing any of the following, state how many against each item

| | |
|---|---|
| Priority Documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patent Form 9/77)* | |
| Request for substantive examination *(Patent Form 10/77)* | |
| Any other documents *(please specify)* | |

11. **I/We request the grant of a patent on the basis of this application**

Signature **STEPHANIE A. LEAROYD 19 JUNE 2002**
***AGENT FOR THE APPLICANTS***

12. Name and daytime telephone number of person to contact in the United Kingdom

**SUE MORTON**

**01438 76 8612**

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## Chemical Compounds

The present invention relates to certain novel compounds. In particular, the present invention relates to compounds that activate human peroxisome proliferator activated receptors ("hPPARs"). The present invention also relates to method for preparing the compounds, their use in medicine, pharmaceutical compositions containing them and methods for the prevention or treatment of PPAR mediated diseases or conditions.

Several independent risk factors have been associated with cardiovascular disease. These include hypertension, increased fibrinogen levels, high levels of triglycerides, elevated LDL cholesterol, elevated total cholesterol, and low levels of HDL cholesterol. HMG CoA reductase inhibitors ("statins") are useful for treating conditions characterized by high LDL-c levels. It has been shown that lowering LDL-c is not sufficient for reducing the risk of cardiovascular disease in some patients, particularly those with normal LDL-c levels. This population pool is identified by the independent risk factor of low HDL-c. The increased risk of cardiovascular disease associated with low HDL-c levels has not yet been totally successfully addressed by drug therapy (Bisgaier, C. L.; Pape, M. E: *Curr. Pharm. Des.* 1998, *4*, 53-70).

Syndrome X (including metabolic syndrome) is loosely defined as a collection of abnormalities including hyperinsulemia, obesity, elevated levels of the following: triglycerides, uric acid, fibrinogen, small dense LDL particles, and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL-c.

NIDDM is described as insulin resistance, which in turn causes anomalous glucose output and a decrease in glucose uptake, by skeletal muscle. These factors eventually lead to impaired glucose tolerance (IGT) and hyperinsulinemia.

Peroxisome Proliferator Activated Receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor superfamily of ligand-activated transcription factors. See, for example Willson T.M. and Wahli, W., *Curr. Opin. Chem. Biol.*, 1, pp235-241 (1997) and Willson T.M. et. al., *J. Med. Chem.*, 43, p527-549 (2000). The binding of agonist ligands to the receptor results in changes in the expression level of mRNA's encoded by PPAR target genes.

Three mammalian Peroxisome Proliferator-Activated Receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-delta (also known as NUC1 or PPAR-beta). These PPARs regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signalling cascade and lipid homeostasis (H. Keller and W. Wahli, *Trends Endocrinol. Metab* 291-296, 4 (1993)).

It has now been reported that the thiazolidinedione class of drugs are potent and selective activators of PPAR-gamma and bind directly to the PPAR-gamma receptor (J. M. Lehmann et. al.,

*J. Biol. Chem.* 12953-12956, 270 (1995)), providing evidence that PPAR-gamma is a possible target for the therapeutic actions of the thiazolidinediones.

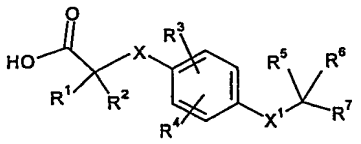
Activators of the nuclear receptor PPARγ, for example rosiglitazone, have been shown in the clinic to enhance insulin-action, reduce serum glucose and have small but significant effects on reducing serum triglyceride levels in patients with Type 2 diabetes. See, for example, D. E. Kelly et al., *Curr. Opin. Endocrinol. Diabetes, 90-96*, 5 (2), (1998); M. D. Johnson et al., *Ann. Pharmacother., 337-348*, 32 (3), (1997); and M. Leutenegger et al., *Curr. Ther. Res., 403-416*, 58 (7), (1997).

The mechanism for this triglyceride lowering effect appears to be predominantly increased clearance of very low density lipoproteins (VLDL) through induction of lipoprotein lipase (LPL) gene expression. See, for example, B. Staels et al., *Arterioscler. Thromb., Vasc. Biol., 1756-1764*, 17 (9), (1997).

Fibrates are a class of drugs which may lower serum triglycerides 20-50%, lower LDLc 10-15%, shift the LDL particle size from the more atherogenic small dense to normal dense LDL, and increase HDLc 10-15%. Experimental evidence indicates that the effects of fibrates on serum lipids are mediated through activation of PPARα. See, for example, B. Staels et al., *Curr. Pharm. Des., 1-14*, 3 (1), (1997). Activation of PPARα results in transcription of enzymes that increase fatty acid catabolism and decrease de-novo fatty acid synthesis in the liver resulting in decreased triglyceride synthesis and VLDL production/secretion. In addition, PPARα activation decreases production of apoC-III. Reduction in apoC-III, an inhibitor of LPL activity, increases clearance of VLDL. See, for example, J. Auwerx et al., *Atherosclerosis, (Shannon, Irel.), S29-S37*, 124 (Suppl), (1996).

Certain compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. See, for example, U.S. Patents 5,847,008 (Doebber et al.) and 5,859,051 (Adams et al.) and PCT publications WO 97/28149 (Leibowitz et al.), WO99/04815 (Shimokawa et al.) and WO 01/00603 (Glaxo Group Ltd.,). Oliver et al *Proc Natl Acad Sci* 98, 5306-5311 (2001) reports that raising of serum triglycerides in the obese rhesus monkey following administration of a PPAR delta agonist

Accordingly the invention provides a compound of formula 1 and pharmaceutically acceptable salts and solvates and hydrolysable esters thereof.



(1)

wherein:

$R^1$ and $R^2$ are independently H or $C_{1-3}$ alkyl;

X represents a O or $(CH_2)_n$ where n is 0, 1 or 2;

$R^3$and $R^4$ independently represent H, $C_{1-3}$ alkyl, $-OCH_3$, $-CF_3$, allyl, or halogen;

$X^1$ represents O, S, $SO_2$, SO, or $CH_2$;

$R^5$ and $R^6$ independently represent hydrogen, $C_{1-6}$ alkyl (including branched alkyl and optionally substituted by one or more halogens or $C_{1-6}$alkoxy), or together with the carbon atom to which they are bonded form a 3-6 membered cycloalkyl ring;

$R^7$ represents a phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1, 2 or 3 moieties selected from the group consisting of halogen, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl, $CF_3$, hydroxy, phenyl (which may be optionally substituted by one or more $C_{1-3}$ alkyl, $-OC_{1-3}$ alkyl, CN, acetyl, hydroxy, halogen or $CF_3$).

In another aspect, the present invention discloses a method for prevention or treatment of a disease or condition mediated by one or more human PPAR alpha, gamma or delta ("hPPARs") comprising administration of a therapeutically effective amount of a compound of this invention. hPPAR mediated diseases or conditions include dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia, syndrome X (as defined in this application this embraces metabolic syndrome), heart failure, hypercholesterolemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, Alzheimers disease and other cognitive disorders, inflammation, epithelial hyperproliferative diseases including eczema and psoriasis and conditions associated with the lung and gut and regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia, and anorexia nervosa. In particular, the compounds of this invention are useful in the treatment and prevention of diabetes and cardiovascular diseases and conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, preferably in association with a pharmaceutically acceptable diluent or carrier.

In another aspect, the present invention provides a compound of the invention for use in therapy, and in particular, in human medicine.

In another aspect, the present invention provides the use of a compound of the invention for the manufacture of a medicament for the treatment of a hPPAR mediated disease or condition.

As used herein, "a compound of the invention" means a compound of formula (I) or a pharmaceutically acceptable salt, or solvate, or hydrolysable ester thereof.

While hydrolyzable esters are included in the scope of this invention, the acids are preferred because the data suggests that while the esters are useful compounds, it may actually be the acids to which they hydrolyse that are the active compounds. Esters that hydrolyse readily can produce the carboxylic acid in the assay conditions or in vivo. Generally the carboxylic acid is active in both the binding and transient transfection assays, while the ester does not usually bind well but is active in the transient transfection assay presumably due to hydrolysis. Preferred hydrolysable esters are $C_{1-6}$ alkyl esters wherein the alkyl group may be straight chain or branched chain. Methyl or ethyl esters are more preferred.

Preferably $R^1$ and $R^2$ are both H or both Me. More preferably both $R^1$ and $R^2$ are H.
Preferably $R^3$ and $R^4$ are independently H or $C_{1-3}$ alkyl. More preferably, at least one of $R^3$ and $R^4$ are hydrogen and when one of $R^4$ and $R^3$ is hydrogen and the other is not, then the one that is not hydrogen is preferably ortho to the depicted moiety X. Most preferably the one that is not hydrogen is methyl.
Preferably X is O.
Preferably $X^1$ is O or S.
Preferably $R^5$ and $R^6$ are independently hydrogen or $C_{1-6}$ alkyl . More preferably one of $R^5$ and $R^6$ is H. Most preferably one of $R^5$ and $R^6$ is H the other is butyl.
Preferably $R^7$ is phenyl or a 6 membered heterocycle selected from pyrimidine, pyridine, pyridazine, pyrazine, each of which is substituted by phenyl (optionally substituted by one or more $C_{1-3}$ alkyl, $CF_3$, halogen). Preferably $R^7$ is substituted by para – $C_6H_4CF_3$.

Preferred compounds of formula (I) include:
[2-Methyl-4-({[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methyl}thio)phenoxy]acetic acid
[2-Methyl-4-({[4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methyl}thio)phenoxy]acetic acid
3-(2-Methyl-4-{[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methoxy}phenyl)propanoic acid
(2-Methyl-4-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]ethyl}phenoxy)acetic acid
{2-Methyl-4-[({6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}methyl)thio]phenoxy}acetic acid
[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]ethyl}thio)phenoxy]acetic acid
[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}thio)phenoxy]acetic acid
2-Methyl-2-{2-methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}propanoic acid
[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]pentyl}oxy)phenoxy]acetic acid
(4-{[1-(4'-Chloro-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid
[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}oxy)phenoxy]acetic acid

(4-{[1-(4'-Chloro-1,1'-biphenyl-4-yl)pentyl]oxy}-2-methylphenoxy)acetic acid

[2-Methyl-4-({(1R)-1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}thio)phenoxy]acetic acid

[2-Methyl-4-({(1S)-1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}thio)phenoxy]acetic acid

{2-Methyl-4-[((1S)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid

{2-Methyl-4-[((1R)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid

{2-Methyl-4-[((1S)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)thio]phenoxy}acetic acid

{2-Methyl-4-[((1R)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)thio]phenoxy}acetic acid

{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)sulfinyl]phenoxy}acetic acid

{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)sulfonyl]phenoxy}acetic acid

{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}acetic acid

[2-Methyl-4-(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}butoxy)phenoxy]acetic acid

{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid

3-{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}propanoic acid

[4-({1-[6-(4-Chlorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

[4-({1-[6-(4-Methoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

[4-({1-[6-(4-Ethoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

[2-Methyl-4-({1-[6-(4-methylphenyl)pyridin-2-yl]pentyl}oxy)phenoxy]acetic acid

[4-({1-[6-(3,4-Dichlorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

{2-Methyl-4-[(1-{6-[3-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid

(2-Methyl-4-{[1-(6-phenylpyridin-2-yl)pentyl]oxy}phenoxy)acetic acid

[4-({1-[6-(4-Acetylphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

[4-({1-[6-(4-Fluorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

[4-({1-[6-(4-Cyanophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid

{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}hexyl)oxy]phenoxy}acetic acid

{2-Methyl-4-[(4-methyl-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid

[2-Methyl-4-(3-methyl-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}butoxy)phenoxy]acetic acid

(4-{[1-(1,1'-Biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid

(4-{[1-(4'-Ethoxy-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid

(4-{[1-(4'-Cyano-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid

(2-Ethyl-4-{[1-(6-phenylpyridin-2-yl)pentyl]oxy}phenoxy)acetic acid

[4-({1-[6-(4-Chlorophenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid

[4-({1-[6-(4-Ethoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid

[4-({1-[6-(4-Cyanophenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid

4-{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}butanoic acid

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in Formula (I) is selected from the preferred, more preferred, or most preferred groups for each variable. Therefore, this invention is intended to include all combinations of preferred and most preferred groups.

Those skilled in the art will recognize that stereocenters exist in compounds of formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of formula (I) and includes not only racemic compounds but this invention is also intended to cover each of these isomers in their racemic, enriched, or purified forms. When a compound of formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis using an optically active catalyst or a catalytic system with optically active ligands or isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds. In particular, in many of the preferred compounds of this invention the carbon atom to which $R^6$ and $R^7$ are bonded is chiral. In some of these chiral compounds the activities at the various PPAR receptors varies between the S and R isomers. Which of these isomers is preferred depends on the particular desired utility of the compound. In other words, even with the same compound, it is possible that the S isomer will be preferred for some uses, while the R isomer will be preferred for others.

The hPPAR agonists of formula (I) may be agonists of only one type ("selective agonists"), agonists for two PPAR subtypes ("dual agonists"), or agonists for all three subtypes ("pan agonists") As used herein, by "agonist", or "activating compound", or "activator", or the like, is meant those compounds which have a pKi of at least 6.0 preferably at least 7.0 to the relevant PPAR, for example hPPARδ in the binding assay described below, and which achieve at least 50% activation of the relevant PPAR relative to the appropriate indicated positive control in the transfection assay described below at concentrations of $10^{-5}$ M or less. More preferably, the agonists of this invention achieve 50% activation of at least one human PPAR in the relevant transfection assay at concentrations of $10^{-6}$ M or less. Preferably the compounds are hPPARδ agonists. More preferably the compounds are selective PPARδ agonists.

It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilised in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium acid addition salts. More specific examples of suitable acid salts include

hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic, naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steroic, tannic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts. Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvents". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I) are within the scope of the invention. References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable salts and solvates.

The compounds of the invention and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides for a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient") with the carrier, which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a other conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulfate. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The tablets may be coated according to methods well-known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to

use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day. The formulations according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

The compound of formula (I) for use in the instant invention may be used in combination with other therapeutic agents for example, statins and/or other lipid lowering drugs for example MTP inhibitors and LDLR upregulators. The compounds of the invention may also be used in combination with antidiabetic agents, e.g. metformin, sulfonylureas and/or PPAR gamma, PPAR alpha or PPAR alpha/gamma agonists (for example thiazolidinediones such as e.g. pioglitazone and rosiglitazone). The compounds may also be used in combination with antihypertensive agents such as angiotensin antagonists e.g. telmisartan, calcium channel antagonists e.g. lacidipine and ACE inhibitors e.g. enalapril. The invention thus provides in a further aspect the

use of a combination comprising a compound of formula (I) with a further therapeutic agent in the treatment of a hPPAR mediated disease.

When the compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

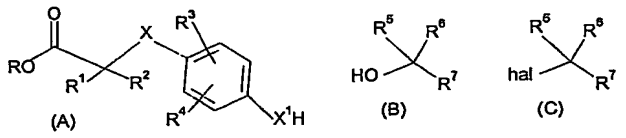
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

When a compound of formula (I) is used in combination with a second therapeutic agent active against the same hPPAR mediated disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Compounds of this invention may be conveniently prepared by a general process wherein a moiety like (A) is coupled to an alcohol (B) using the Mitsunobu protocol (O. Mitsunobu, 1981, Synthesis p1) or by alklylaton of (A) using a suitable non nucleophilic base such as $K_2CO_3$, $Cs_2CO_3$ or NaH, with an alkyl halide (C).

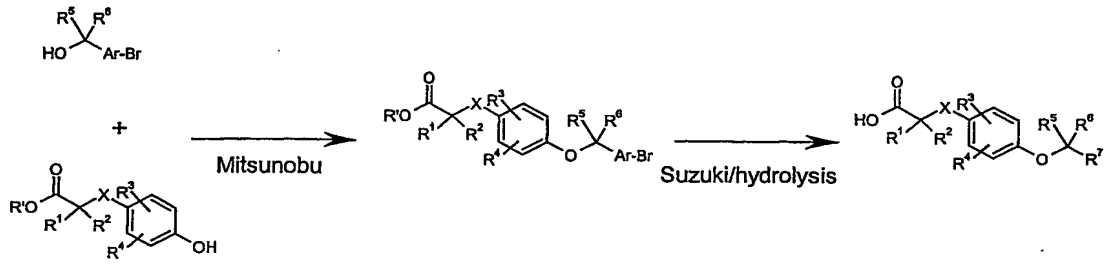
Note this synthesis is preferably carried out with the acid group protected by R. Preferably R is $C_{1-6}$alkyl which can be hydrolysed to give an acid of formula (1), or if readily hydrolyzable, the resulting ester can be administered.



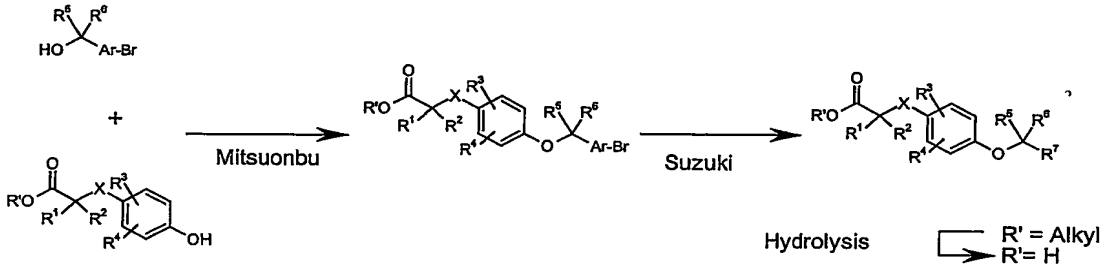

Intermediates of formulae (A), (B), and (C) are commercially available or may be synthesised as outlined below.

For example, when $X^1$ is O, the following synthetic schemes may be followed.

**Route O1 Mitsunobu followed by Suzuki with concomitant hydrolysis**

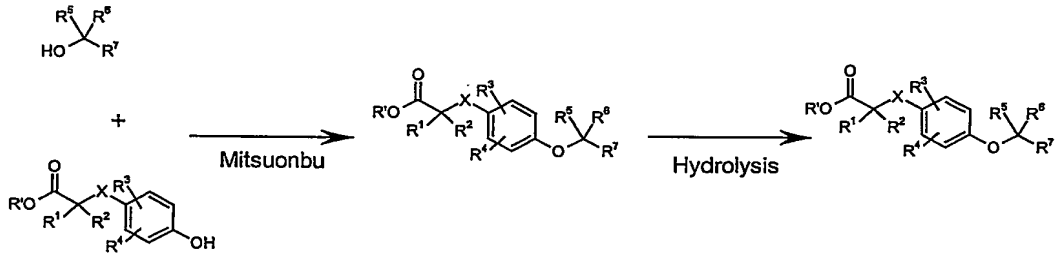



**Route O2 Mitsunobu followed by Suzuki and then hydrolysis**




**Route O3**

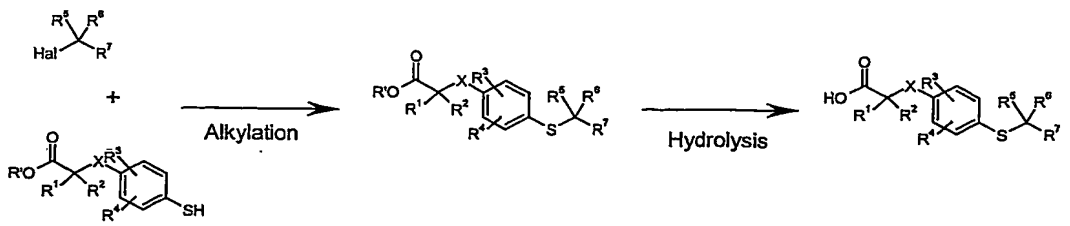
Mitsunobu followed by hydrolysis




When $X^1$ represents S, the following synthetic schemes may be followed:

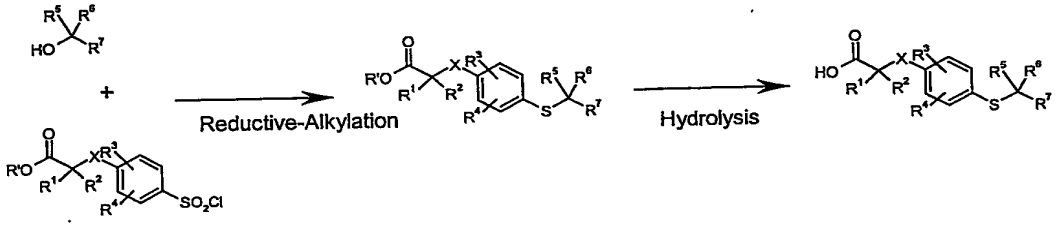
**Route S1**

Alkylation followed by hydrolysis



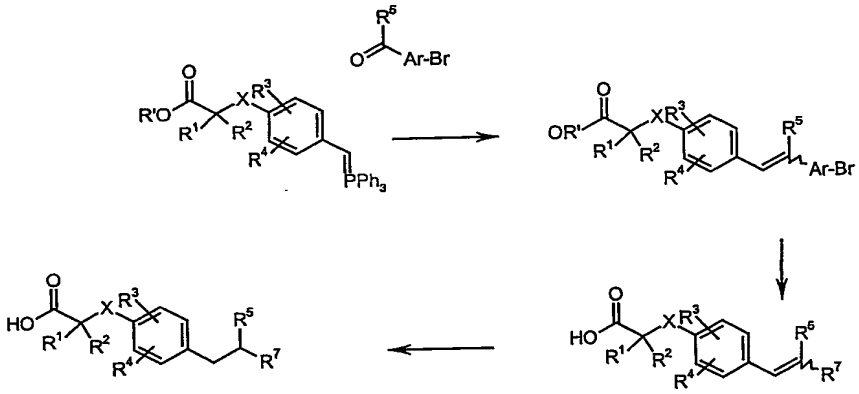
**Route S2**

Reductive alkylation followed by hydrolysis




When $X^1$ represents $CH_2$ the following scheme may be followed:

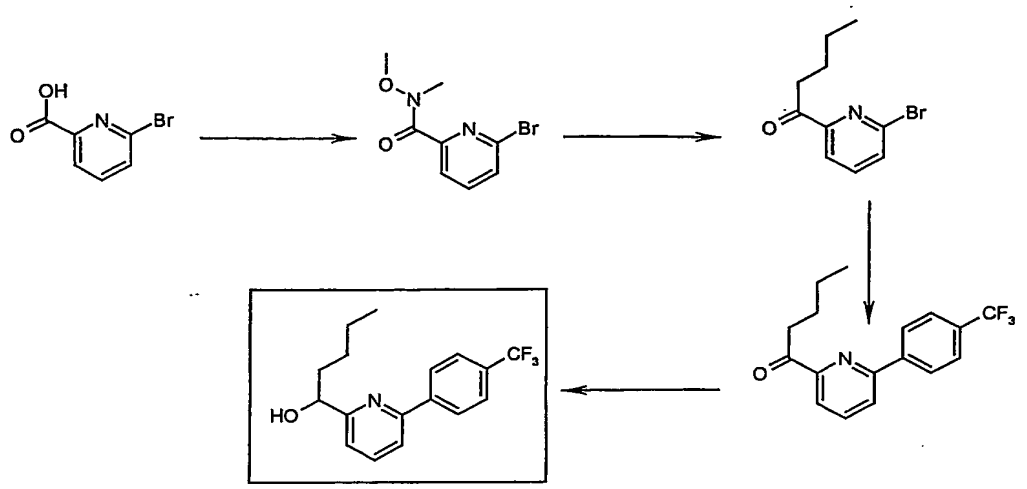
**Route C1**



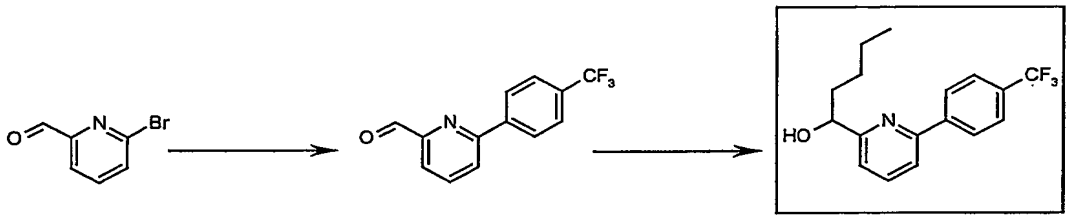

Wittig, Suzuki, hydrolysis, hydrogenation

**Alcohol intermediate 4**

**Method A**



**Method B**



Other intermediates may be prepared as described in text below or in published literature e.g. WO 01/00603 and their synthesis will be apparent to a person skilled in the art.

The following illustrates Intermediates and Examples of Formula 1 which should not be construed as constituting a limitation thereto.

**General purification and analytical methods**

LC/MS refers to analysis by analytical HPLC which was conducted on a Supelcosil LCABZ+PLUS column (3µm, 3.3cm x 4.6mm ID) eluting with 0.1% $HCO_2H$ and 0.01 M ammonium acetate in water (solvent A), and 95% acetonitrile and 0.05% $HCO_2H$ in water (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0→100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 100→0%B at a flow rate of 3 ml/minute. The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give $[M+H]^+$ and $[M+NH_4]^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $[M-H]^-$ molecular ion] modes.

$^1$H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer.

Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KP-Sil™ silica.

Mass directed auto-prep HPLC refers to the method where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% $HCO_2H$ in water and 95% MeCN, 5% water (0.5% $HCO_2H$) utilising the following gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a flow rate of 8ml/minute. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrophobic frits refers to filtration tubes sold by Whatman.

SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd.

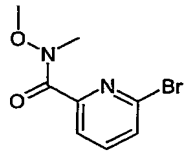
TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 $F_{254}$.

Abbreviations :

| | |
|---|---|
| TLC : | thin layer chromatography |
| DMSO-$d^6$ : | deuterated dimethylsulfoxide |
| $CDCl_3$ : | deuterated chloroform |
| MeOD-$d^4$ : | deuterated methanol |
| AcOH : | acetic acid |
| ADDM : | 1,1'-(azodicarboxylic)dimorpholide |
| ADDP : | 1,1'-(azodicarbonyl)dipiperidine |
| CDI : | 1,1'-carbonyldiimidazole |
| DCM : | dichloromethane |
| 4-DMAP : | 4-dimethylaminopyridine |
| DMF : | N,N-dimethylformamide |
| EDC : | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| $Et_2O$ : | diethyl ether |
| EtOAc : | ethyl acetate |

| | |
|---|---|
| MeCN : | acetonitrile |
| MeOH : | methanol |
| $n$Bu$_3$P : | tributylphosphine |
| $R_t$ : | retention time |
| TBAF : | tetrabutylammonium fluoride |
| THF : | tetrahydrofuran |
| br : | broad |
| s : | singlet |
| d : | doublet |
| dd : | doublet of doublets |
| t : | triplet |
| q : | quartet |
| m : | multiplet |
| rt : | room temperature |

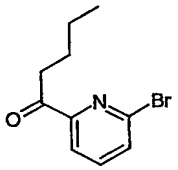
**Intermediate 1**



To a slurry of 6-bromopicolinic acid (5.44 g, 26.93 mmol) in DCM (100 mL) was added a solution of CDI (5.67 g, 34.97 mmol) in DCM (70 mL) drop-wise over 15 minutes under nitrogen. The solution cleared a little during the addition but remained cloudy and after 1 hour at rt the mixture was treated drop-wise over 15 minutes with N,O-dimethylhydroxylamine [solution in DCM prepared by treating N,O-dimethylhydroxylamine hydrochloride (5.35 g, 53.82 mmol) with aqueous NaOH (2M, 100 mL) and extracting with DCM (2 x 100 mL)]. The mixture cleared during the addition and the resulting clear pale yellow solution was left to stir under nitrogen for 20 hours. The mixture was then reduced under vacuum and the residue partitioned between EtOAc (125 mL) and saturated aqueous $NaHCO_3$ (125 mL). The layers were then separated and the organic layer washed with brine (125 mL), dried ($MgSO_4$), filtered and reduced to give intermediate 1 as a yellow oil (5.29 g, 80%).

LC/MS: m/z 245.0 $[M+H]^+$, $R_t$ 2.27 min.

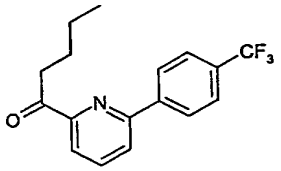
**Intermediate 2**



To a solution of intermediate 1 (5.29 g, 21.58 mmol) in dry THF (120 mL) at –78°C (dry ice/acetone bath) under nitrogen was added *n*BuMgCl (15.2 mL of a 20%wt solution in THF/toluene, 25.84 mmol) drop-wise over 15 minutes. The resulting yellow mixture was stirred at this temperature for 1 hour and was then allowed to warm to 0°C (ice/water bath) slowly over 1.5 hours and then to rt over 18 hours. The yellow cloudy mixture was then added portion-wise to a stirred solution of aqueous HCl (2M, 200 mL) and the resulting mixture partitioned with EtOAc (200 mL) and the layers separated. The aqueous was re-extracted with EtOAc (200 mL) and the combined organic layer washed with brine (300 mL), dried ($MgSO_4$) filtered and reduced to give a yellow/orange oil. Purification by Biotage™ chromatography (silica) eluting with cyclohexane : EtOAc (gradient 20:1 to 1:2) afforded intermediate 2 (2.51 g, 48%).

LC/MS: m/z 242.0 $[M+H]^+$, $R_t$ 3.57 min.

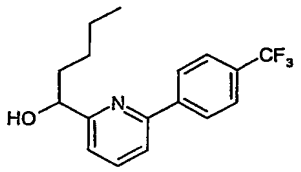
**Intermediate 3**



A solution of intermediate 2 (2.51 g, 10.37 mmol) in DME (13 mL) was treated with 4-(triflouromethyl)benzeneboronic acid (2.36 g, 12.43 mmol), $Pd(PPh_3)_4$ (1.19 g, 1.03 mmol) and then a slurry of $Na_2CO_3$ (3.29 g, 31.04 mmol) in water (13 mL). The resulting mixture was then heated to reflux over 30 minutes and then stirred at this temperature for 17 hours. The mixture was then allowed to cool to rt and was reduced and the residue partitioned between EtOAc (200 mL) and water (200 mL). The aqueous was re-extracted with EtOAc (100 mL) and the combined organic layer washed with saturated aqueous $NaHCO_3$ (250 mL), brine (250 mL), dried ($MgSO_4$), filtered and reduced to give a brown orange solid residue. Purification by Biotage™ chromatography (silica) eluting with cyclohexane : EtOAc (gradient 1:0 to 10:1) afforded intermediate 3 as a white solid (3.02 g, 95%).

LC/MS: m/z 308.2 $[M+H]^+$, $R_t$ 4.14 min.

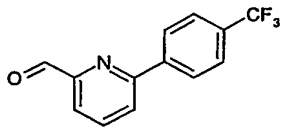
**Intermediate 4 (Method A)**



A mixture of intermediate 3 (2.80 g, 9.11 mmol) in THF (61 mL) at 0°C (ice/water bath) was treated drop-wise with a mixture of sodium borohydride (689 mg, 18.21 mmol) in water (11 mL) over 5-10 minutes. The resulting mixture was stirred at this temperature for 2.5 hours and was then partitioned between EtOAc (200 mL) and water (200 mL) and the layers separated. The aqueous was re-extracted with EtOAc (200 mL) and the combined organic layer washed with brine (250 mL), dried ($MgSO_4$), filtered and reduced. Purification by Biotage™ chromatography (silica) eluting with cyclohexane : EtOAc (gradient 20:1 to 5:1) afforded intermediate 4 as a colourless oil (2.81 g, 100%).

LC/MS: m/z 310.2 $[M+H]^+$, $R_t$ 3.87 min.

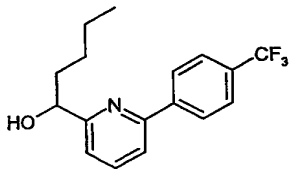
**Intermediate 5**



A solution of 6-bromo-2-pyridinecarboxaldehyde (512 mg, 2.75 mmol) and 4-(triflouromethyl)benzeneboronic acid (522 mg, 2.75 mmol) in DME (46 mL) was treated a slurry of $Na_2CO_3$ (875 mg, 8.26 mmol) in water (23 mL) followed by $Pd(PPh_3)_4$ (64 mg, 0.06 mmol). The resulting mixture was then heated to reflux, under nitrogen over 30 minutes and then stirred at this temperature for 17 hours. The mixture was then allowed to cool to rt, was reduced under vacuum and the residue partitioned between EtOAc (50 mL) and water (50 mL) and the layers separated. The aqueous was re-extracted with EtOAc (100 mL) and the combined organic layer washed with brine (100 mL), dried ($MgSO_4$), filtered and reduced to give a yellow solid residue. Purification by SPE (silica) eluting with cyclohexane : EtOAc (gradient 1:0 to 10:1) afforded intermediate 5 as a yellow foam (565 mg, 82%).

LC/MS: m/z 251.9 $[M+H]^+$, $R_t$ 3.57 min.

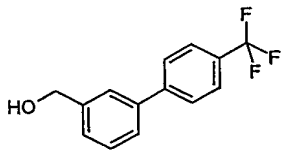
**Intermediate 4 (Method B)**




A solution of intermediate 5 (2.50 g, 9.95 mmol) in dry THF (100 mL) was cooled to 0°C (ice/water bath) and treated with *n*BuLi (6.8 mL of a 1.6M solution in hexanes, 10.88 mmol) under nitrogen drop-wise over 20 minutes. The resulting deep red coloured solution was stirred at 0°C for 1.5 hours and then quenched by the addition of aqueous HCl (2M, 10 mL) and allowed to warm to rt over about 20 minutes. The solvents were then removed under vacuum and the residue partitioned between EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (150 mL) and the layers separated. The aqueous was re-extracted with EtOAc (100 mL) and the combined organic layer washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and reduced to give a pale yellow foam. Purification by Biotage™ chromatography (silica) eluting with cyclohexane : EtOAc (gradient 100:1 to 0:1) afforded intermediate 4 as a pale yellow oil (1.99 g, 65%).

LC/MS: m/z 310.2 $[M+H]^+$, $R_t$ 3.87 min.

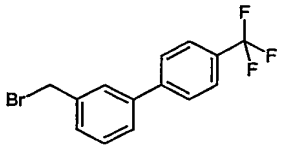
**Intermediate 6**




A mixture 3-bromobenzyl alcohol (500 mg, 2.70 mmol), 4-(triflouromethyl)benzeneboronic acid (1.01 g, 5.35 mmol), $Pd(PPh_3)_4$ (68 mg, 0.06 mmol) and $Na_2CO_3$ (740 mg, 7.02 mmol) in a mixture of DME (20 mL) and water (10 mL) was heated at reflux for 3 hours. The mixture was allowed to cool to rt, and then partitioned between EtOAc and water. The layers were separated and the aqueous re-extracted with EtOAc (2x) and the combined organic layer washed with water and then brine, dried ($Na_2SO_4$), filtered and reduced to give an oil. Purification by flash chromatography (silica) eluting with cyclohexane : EtOAc (5:2) afforded intermediate 6 as a clear oil which crystallised on standing (654 mg, 97%).

LC/MS: $R_t$ 3.58 min, no molecular ion observed.

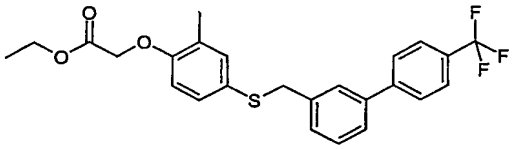
**Intermediate 7**



A solution of intermediate 6 (177 mg, 0.70 mmol) in dry DCM (10 mL) was cooled to 0°C (ice/water bath) under nitrogen and treated with $CBr_4$ (256 mg, 0.77 mmol) in one portion. $PPh_3$ (202 mg, 0.77 mmol) was then added portion-wise and the resulting mixture stirred for 1 hour at this temperature and was then allowed to warm to rt. The resulting mixture was then reduced and the residue purified directly by SPE (silica, 10 g cartridge) eluting with cyclohexane : DCM to intermediate 7 as a colourless oil.

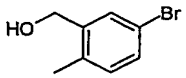
LC/MS: $R_t$ 3.94 min, no molecular ion observed.

**Intermediate 8**



A mixture of intermediate 7 (200 mg, 0.63 mmol), ethyl (4-mercapto-2-methylphenoxy)acetate (144 mg, 0.63 mmol) and polymer supported diisopropylethylamine (3mmol/g, 423 mg, 1.27 mmol) in DCM (20 mL) was stirred at rt overnight. TLC (cyclohexane : DCM 1:1) indicated bromide still remaining so more thiol (100 mg, 0.44 mmol) was added and after 3 hours no change was observed by TLC. The mixture was then filtered, reduced and purified using SPE (silica, 10 g cartridge). The residue was dissolved in DCM (10 mL) and treated with polymer supported isocyante resin (1.43 mmol/g. 2 g, 2.46 mmol) and stirred at rt overnight. The mixture was then filtered, washing with DCM and reduced to give intermediate 8.

**Intermediate 9**

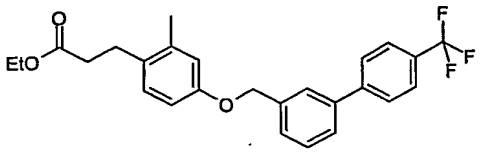


Borane (10.80 mL of a 1M solution in THF, 10.80 mmol) was added to a cooled solution of 5-bromo-2-methyl-benzoic acid (116 mg, 0.54 mmol) in THF (15 mL), under nitrogen, at 0°C (ice water bath) and the resulting mixture allowed to warm to rt overnight. The mixture was then treated with MeOH (10 mL) followed by aqueous HCl (2M, 20 mL) and the mixture stirred for

about 15 minutes, concentrated under vacuum and then partitioned with EtOAc. The organic layer was washed with aqueous HCl (2M), water and brine, dried ($MgSO_4$), filtered and reduced to give the intermediate 9 as a colourless oil (90 mg, 83%).

LC/MS: $R_t$ 3.09 min, no molecular ion observed.

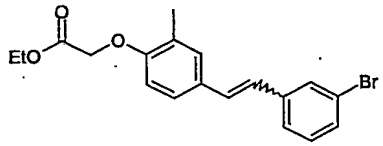
**Intermediate 10**



To a solution of intermediate 6 (121 mg, 0.48 mmol) in dry THF (5 mL) under nitrogen at 0°C (ice/water bath) was added $n$Bu$_3$P (240 µL, 0.96 mmol) followed by ethyl 3-(4-hydroxy-2-methylphenyl)propanoate (100 mg, 0.48 mmol) and then ADDM (246 mg, 0.96 mmol) portion-wise. The mixture was stirred at 0°C for 1 hour, allowed to warm to rt over 21 hours and then partitioned between water and EtOAc, and the layers separated. The aqueous layer was then extracted with EtOAc and the combined organic extract washed with water and then brine, dried ($Na_2SO_4$) and the solvent removed under vacuum. Purification by flash chromatography (silica) eluting with cyclohexane : EtOAc (15:1) afforded intermediate 10 as a clear oil (141 mg, 66%).

LC/MS: $R_t$ 4.43 min, no molecular ion observed.

**Intermediate 11**

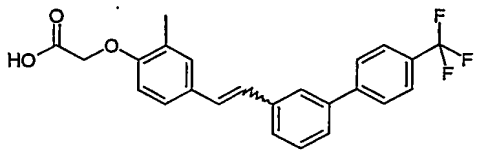


A suspension of [4-(2-ethoxy-2-oxoethoxy)-3-methylbenzyl](triphenyl)phosphonium chloride (500 mg, 0.99 mmol) in dry THF (10 mL) was cooled to 0°C (ice/water bath) and treated with NaH (44 mg of a 60% dispersion in mineral oil, 1.10 mmol) portion-wise over 5 minutes. The resulting yellow suspension was stirred for 15 minutes and was then treated with 3-bromobenzaldehyde (184 mg, 0.99 mmol) in dry THF (5 mL). The resulting white suspension was allowed to warm to rt over 3.5 hours and was then heated at reflux for 1 hour. The reaction mixture was then allowed to cool to rt, stirred overnight and was then reduced under vacuum. The residue was then partitioned between $CHCl_3$ (20 mL) and water (20 mL) and the layers separated. The cloudy organic layer was dried through a hydrophobic frit and then concentrated to a cream coloured

gum (700 mg). Purification by SPE (silica) eluting with cyclohexane : EtOAc (9:1) afforded intermediate 11 (mixture of *E*:*Z* isomers) (258 mg, 69%).

LC/MS: $R_t$ 4.23 min and 4.31 min, no molecular ions observed.

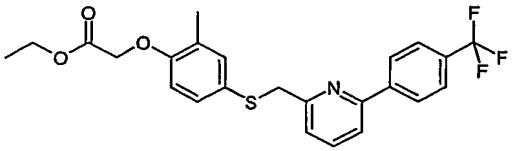
**Intermediate 12**



Intermediate 11 (150 mg, 0.40 mmol), $Na_2CO_3$ (106 mg, 1.00 mmol), 4-(triflouromethyl)benzeneboronic acid (83.5 mg, 0.44 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was dissolved in DME and water (2:1, 6 mL) and the mixture heated at reflux for 4 hours. The mixture was allowed to cool to rt, was concentrated under reduced pressure and the residue partitioned between EtOAc (15 mL) and water (15 mL). The aqueous layer was then acidified with aqueous HCl (1N) and extracted with EtOAc and the combined organic layers dried ($MgSO_4$), filtered and reduced to give intermediate 12 (94 mg).

LC/MS: m/z 411 $[M-H]^+$, $R_t$ 4.45 min and 4.67 min.

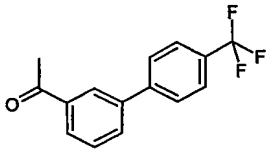
**Intermediate 13**



A solution of the 2-(bromomethyl)-6-[4-(trifluoromethyl)phenyl]pyridine (238 mg, 0.75 mmol), ethyl (4-mercapto-2-methylphenoxy)acetate (84 mg, 0.37 mmol) and $K_2CO_3$ (57 mg, 0.41 mmol) in MeCN (5 mL) was stirred at rt, under nitrogen overnight. The mixture was then partitioned between water and EtOAc and the layers separated. The organic layer was then washed with water and brine, dried ($MgSO_4$), filtered and reduced. Purification by SPE (silica, 2g cartridge) eluting with $CHCl_3$ : cyclohexane (5:1) afforded intermediate 13 (160 mg).

LC/MS: m/z 462.3 $[M+H]^+$, $R_t$ 4.10 min.

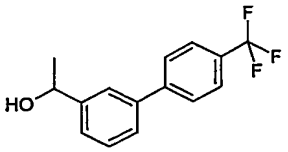
**Intermediate 14**



A solution of 3-bromoacetophenone (661 µL, 5.00 mmol) and 4-(triflouromethyl)benzeneboronic acid (950 mg, 5.00 mmol) in DME (50 mL) was added $Na_2CO_3$ (1.32 g, 12.50 mmol) and $Pd(PPh_3)_4$ (283 mg, 0.24 mmol) and water (25 mL). The mixture was then stirred at 100°C for 20 hours, diluted with water and extracted with EtOAc. The organic layer was then washed with brine, dried ($Na_2SO_4$), filtered and reduced. Purification by flash chromatography (silica) eluting with petrol : EtOAc (gradient 19:1 to 9:1) afforded intermediate 14 (1.01 g, 83%).

LC/MS: $R_t$ 3.62 min, no molecular ion observed.

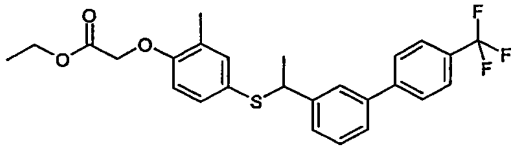
**Intermediate 15**



A mixture of intermediate 14 (300 mg, 1.14 mmol) in water (1 mL) and EtOH (5 mL) was treated portion-wise with sodium borohydride (57 mg, 1.50 mmol) and then stirred at rt for 1.5 hours. The reaction was then quenched by the addition of saturated aqueous $NH_4Cl$, diluted with $CHCl_3$ and the layers separated. The organic layer was then dried ($Na_2SO_4$), filtered and reduced to give intermediate 15 (274 mg, 91%).

LC/MS: $R_t$ 3.50 min, no molecular ion observed.

**Intermediate 16**

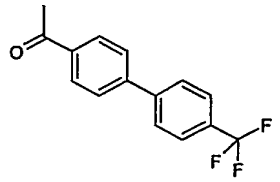


Zinc (229 mg, 3.50 mmol) was added to EtOAc (10 mL) followed by AcOH (115 µM, 2.00 mmol) and ethyl [4-(chlorosulfonyl)-2-methylphenoxy]acetate (293 mg, 1.00 mmol). After 2 hours, dichlorodimethylsilane (258 mg, 2.00 mmol) was added followed by intermediate 15 (266 mg,

1.00 mmol) and the mixture stirred for a further 1 hour and then heated at 80°C for 5 hours. The mixture was then cooled, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, saturated aqueous $NH_4Cl$, water and brine, and then reduced. Purification by Biotage™ chromatography (silica) eluting with petrol : EtOAc (9:1) afforded intermediate 16 as a colourless oil (238 mg, 50%).

LC/MS: m/z 492.2 $[M+NH_4]^+$, $R_t$ 4.28 min.

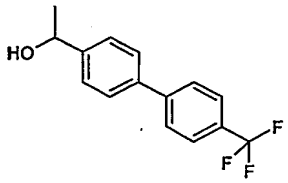
**Intermediate 17**



Prepared according to the procedure used for the preparation of intermediate 14, starting from 4-bromoacetophenone (661 µL, 5.00 mmol), to give, after purification by Biotage™ chromatography (silica) eluting with petrol : EtOAc (8:1), intermediate 17 (1.10 g, 83%).

LC/MS: $R_t$ 3.63 min, no molecular ion observed.

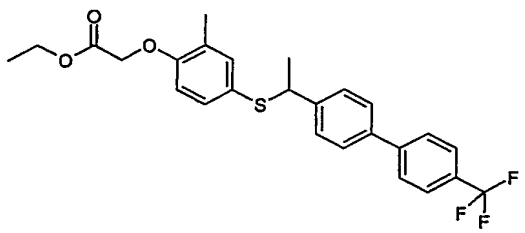
**Intermediate 18**



Prepared from intermediate 17 (305 mg, 1.15 mmol) according to the procedure used for the preparation of intermediate 15 to give intermediate 18 (324 mg, 100%).

LC/MS: $R_t$ 3.54 min, no molecular ion observed.

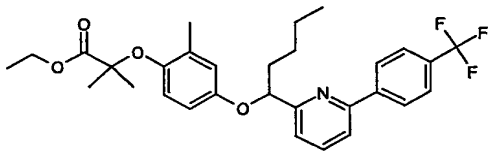
**Intermediate 19**



Prepared from intermediate 18 (324 mg, 1.15 mmol) according to the procedure used for the preparation of intermediate 16, to give, after purification by Biotage™ chromatography (silica) eluting with petrol : EtOAc (8:1), intermediate 19 as a colourless oil (333 mg, 61%).

LC/MS: m/z 492.2 $[M+NH_4]^+$, $R_t$ 4.31 min.

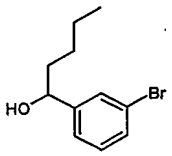
**Intermediate 20**



To a solution of $n$Bu$_3$P (47 µL, 0.19 mmol) in dry THF (2 mL), at 0°C (ice/water bath) under nitrogen was added DIAD (37 mL, 0.19 mmol). After stirring for 10 minutes intermediate 4 (50 mg, 0.16 mmol) was added, followed after another 20 minutes by ethyl 2-(4-hydroxy-2-methylphenoxy)-2-methylpropanoate (39 mg, 0.16 mmol). The mixture was then allowed to warm to rt over 16 hours and was then reduced under vacuum and the residue partitioned between EtOAc and water. The layers were separated and the organic layer washed with water (2 x) then brine, dried ($Na_2SO_4$) and reduced to give a brown gum. Purification by Biotage™ chromatography (silica, 40 g cartridge) eluting with cyclohexane : EtOAc (19:1) afforded intermediate 20 as a colourless gum (9 mg, 11%).

LC/MS: m/z 530.3 $[M+H]^+$, $R_t$ 4.61 min.

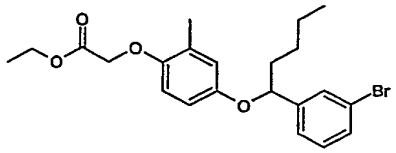
**Intermediate 21**



To 3-bromobenzaldehyde (5.00 g, 27.02 mmol) in dry THF (100 mL), under nitrogen at –78°C (dry ice/acetone bath) was added $n$BuMgCl (16.2 mL of a 2.0M solution in THF, 0.032 mol) and the reaction stirred for 1 hour at –78°C and then allowed to warm to rt overnight. The reaction was then quenched with water, extracted with EtOAc and the layers separated. The organic layer was washed with water then brine, dried ($Na_2SO_4$) and reduced under vacuum to give a colourless oil. Purification by Biotage™ chromatography (silica, 90 g cartridge) eluting with cyclohexane : EtOAc 9:1 afforded intermediate 21 as a colourless oil (4.07 g, 62%).

LC/MS: $R_t$ 3.49 min, no molecular ion observed.

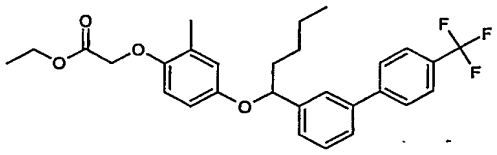
**Intermediate 22**



To a solution of intermediate 21 (1.00 g, 4.11 mmol) in dry THF (40 mL) at 0°C was added ethyl (4-hydroxy-2-methylphenoxy)acetate (865 mg, 4.11 mmol), $PPh_3$ (1.30 g, 4.94 mmol) and ADDP (1.25 g, 4.94 mmol) and the reaction stirred for 30 minutes and then allowed to warm to rt overnight. The mixture was then reduced under vacuum and the residue partitioned between EtOAc and water and the layers separated. The organic layer was washed with water (2 x) then brine, dried ($Na_2SO_4$) and reduced under vacuum to give a brown oil. Purification by Biotage™ chromatography (silica, 90 g cartridge) eluting with petroleum ether 40-60°C : EtOAc (gradient 1:0 to 9:1) afforded the intermediate 22 as colourless oil (1.15 g, 64%).

LC/MS: 454.0/455.1 $[M+NH_4]^+$, $R_t$ 4.28 min.

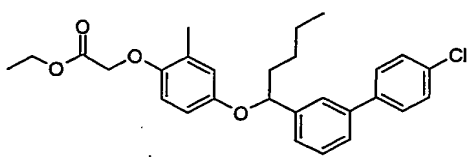
**Intermediate 23**



Intermediate 22 (200 mg, 0.46 mmol) was dissolved in dry THF (3 mL), and treated with 4-(trifluoromethyl)benzeneboronic acid (104 mg, 0.55 mmol), $Pd(PPh_3)_4$ (53 mg, 0.046 mmol) and sodium carbonate (146 mg, 1.38 mmol) in water (2 mL). The mixture was then heated at 70°C for 3 hours, cooled to rt and partitioned between EtOAc and water. The layers were separated and the organic layer washed with brine, dried ($Na_2SO_4$) and concentrated to give a brown oil. Purification by Biotage™ chromatography (silica, 40 g cartridge) eluting with petroleum ether 40-60°C : EtOAc (19:1) afforded intermediate 23 as a colourless gum (142 mg, 62%).

LC/MS: m/z 518.2 $[M+NH_4]^+$, $R_t$ 4.55 min.

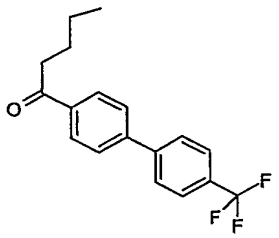
**Intermediate 24**



Prepared according to the procedure used for the preparation of intermediate 23, starting from intermediate 22 (200 mg, 0.46 mmol) and 4-chlorobenzene boronic acid (86 mg, 0.55 mmol) to give, after purification by Biotage™ chromatography (silica, 40 g cartridge) eluting with petroleum ether 40-60°C : EtOAc (19:1), intermediate 24 (137 mg, 64%).

LC/MS: m/z 484.2 $[M+NH_4]^+$, $R_t$ 4.55 min.

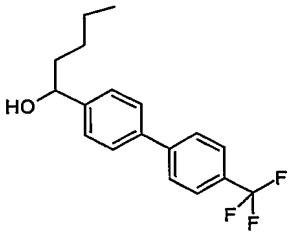
**Intermediate 25**



To a solution of 4-bromovalerophenone (1.00 g, 4.15 mmol) in DME (20 mL) and water (10 mL) was added 4-(trifluoromethyl)benzeneboronic acid (870 mg, 4.57 mmol) and $Na_2CO_3$ (1.10 g, 10.38 mmol). After 10 minutes under nitrogen, $Pd(PPh_3)_4$ (480 mg, 0.42 mmol) was added portion-wise, and the mixture heated to reflux and stirred under nitrogen for 2 hours. The reaction mixture was then allowed to cool to rt and the solvents removed under vacuum. The resulting residue was partitioned between water and EtOAc, the layers separated and the aqueous re-extracted with EtOAc (3 x 30mL). The combined organic extract was separated and dried ($MgSO_4$), and the solvent removed under vacuum. Purification by flash chromatography (silica), eluting with cyclohexane : EtOAc (19:1) afforded intermediate 25 as a white solid (850 mg, 67%).

LC/MS: m/z 307.1 $[M+H]^+$, $R_t$ 4.16 min.

**Intermediate 26**

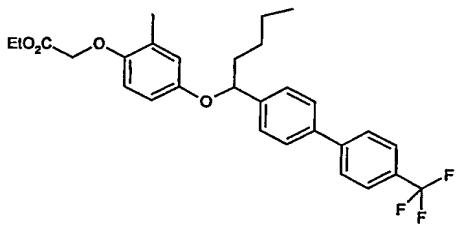


To a solution of intermediate 25 (500 mg, 1.63 mmol) in THF (16 mL) and water (8 mL) under nitrogen at 0°C (ice/water bath) was added sodium borohydride (74 mg, 1.96 mmol) portion-wise. After stirring the mixture for 1 hour at rt, the reaction was diluted with water (30 mL) and extracted into EtOAc (3 x 30 mL). The combined organic extract was separated, dried

($MgSO_4$) and reduced under vacuum to afford intermediate 26 as a colourless gum (490 mg, 97%).

LC/MS: $R_t$ 3.96 min, no molecular ion observed.

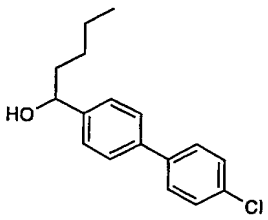
**Intermediate 27**



To a solution of intermediate 26 (250 mg, 0.81 mmol) in dry THF (20 mL) under nitrogen at 0°C (ice/water bath) was added $n$Bu$_3$P (0.41mL, 1.64 mmol), followed by ethyl (4-hydroxy-2-methylphenoxy)acetate (170 mg, 0.81 mmol) and ADDM (420 mg, 1.64 mmol) portion-wise. After stirring the mixture for 18 hours at rt under nitrogen the solvent was removed under vacuum. The residue was partitioned between water and EtOAc and the aqueous re-extracted with EtOAc (3 x 30 mL). The organic combined extract was dried ($MgSO_4$) and then reduced under vacuum. Purification by flash chromatography (silica), eluting with cyclohexane : EtOAc (9:1) afforded intermediate 27 as a colourless gum (310 mg, 76%).

LC/MS: m/z 518.2 $[M+NH_4]^+$, $R_t$ 4.55 min.

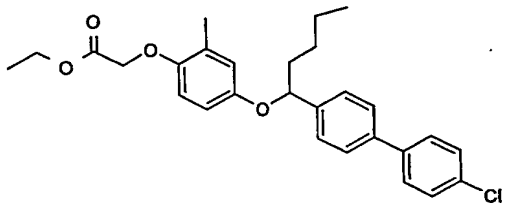
**Intermediate 28**



To a solution of 4-(4-chlorophenyl)benzaldehyde (200 mg, 0.92 mmol) in anhydrous THF (10 mL) under nitrogen at -78°C (dry ice/acetone) was added $n$BuMgCl (550 µL of a 2M solution in THF, 1.10 mmol). The reaction mixture was stirred at -78°C for 1 hour and then at rt for 18 hours. The reaction was quenched by cautious addition of water (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extract was then dried ($MgSO_4$) and reduced under vacuum. Purification by flash chromatography (silica), eluting with cyclohexane : EtOAc (9:1) afforded the intermediate 28 as a colourless gum (140 mg, 55%).

LC/MS: $R_t$ 3.98 min, no molecular ion observed.

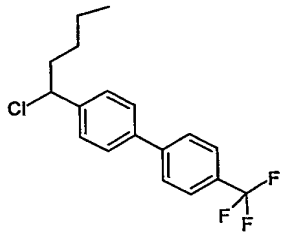
**Intermediate 29**



To a solution of intermediate 28 (140 mg, 0.51 mmol) in dry THF (15 mL) under nitrogen at 0°C (ice/water bath) was added $n$Bu$_3$P (250 µL, 1.02 mmol), followed by ethyl (4-hydroxy-2-methylphenoxy)acetate (110 mg, 0.52 mmol) and ADDP (260 mg, 1.03 mmol) portion-wise. After stirring the mixture for 18 hours at rt under nitrogen the solvent was removed under vacuum. The residue was partitioned between water and EtOAc and extracted with EtOAc (3 x 30 mL). The organic extract was separated and dried ($MgSO_4$) and the solvent removed under vacuum. Purification by flash chromatography (silica) eluting with cyclohexane : EtOAc (9:1) afforded the intermediate 29 as a colourless gum (150 mg, 63%).

LC/MS: m/z 484.2 $[M+NH_4]^+$, $R_t$ 4.51 min.

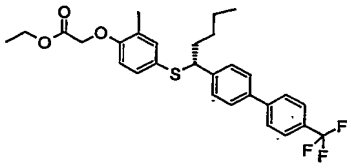
**Intermediate 30**



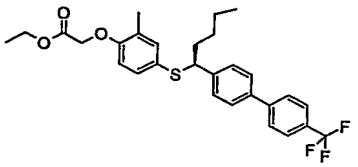
To a solution of intermediate 26 (250 mg, 0.81 mmol) in dry DCM (15 mL) under nitrogen at 0°C (ice/water bath) was added thionyl chloride (590 µL, 8.09 mmol) drop-wise. After stirring the mixture for 30 minutes at rt under nitrogen, the reaction was quenched by cautious addition of saturated aqueous $NaHCO_3$ (20 mL) and extracted with DCM (3 x 30 mL). The organic extract was separated, washed with brine, dried ($MgSO_4$) and the solvents removed under vacuum to afford intermediate 30 as a yellow gum (251 mg, 95%).

LC/MS: $R_t$ 4.42 min, no molecular ion observed.

**Intermediates 31 and 32**



Intermediate 31



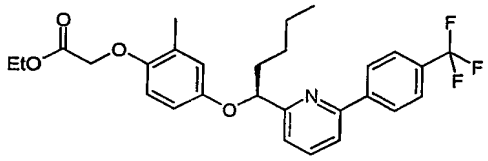
Intermediate 32

To a solution of ethyl (4-mercapto-2-methylphenoxy)acetate (170 mg, 0.75 mmol) in anhydrous MeCN (15 mL) under nitrogen was added intermediate 30 (500 mg, 1.53 mmol) and caesium carbonate (500 mg, 1.53 mmol). After 18 hours stirring under nitrogen at room temperature, the reaction mixture was filtered and the solvent removed under vacuum. Purification by flash chromatography (silica), eluting with cyclohexane : EtOAc (9:1) afforded a colourless gum (230 mg, 59%).

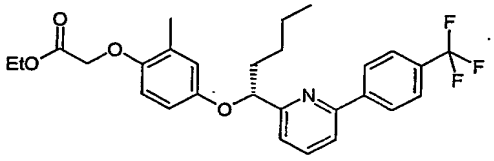
LC/MS: m/z 517.1 $[M+H]^+$, $R_t$ 4.64 min.

Separation of a 20 mg sample by chiral HPLC (2 x 25cm chiralpak A) eluting with 5% IPA/cycloheptane, 15ml/min, wavelength 215nm afforded intermediate 31 as a colourless oil (10 mg, $R_t$ 8.2 min) and intermediate 32 as a colourless oil (9 mg, $R_t$ 9.8 min).

**Intermediate 33 and 34**



Intermediate 33



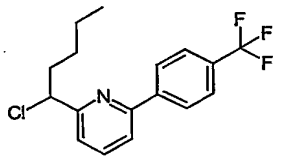
Intermediate 34

To a solution of intermediate 4 (711 mg, 2.30 mmol) in dry THF (46 mL) at 0°C (ice/water bath) was added ethyl (4-hydroxy-2-methylphenoxy)acetate (483 mg, 2.30 mmol) followed one minute later by ADDM (1.18 g, 4.60 mmol) in one portion. The resulting slightly cloudy orange mixture was stirred at rt for 2-3 mins and the treated with $n$Bu$_3$P (1.15 mL, 4.61 mmol) drop-wise over about 4 minutes to give a clear pale yellow solution. After 2 hours of slow warming, the solution had become slightly cloudy and was allowed to warm further to rt over 20 hours. The resulting cloudy mixture was then reduced under vacuum and the residue partitioned between EtOAc (150 mL) and water (150 mL) and the layers separated. The aqueous was re-extracted with EtOAc (150 mL) and the combined organic layers washed with brine (250 mL), dried ($MgSO_4$), filtered and reduced to give an oil. Purification by SPE (silica) eluting with cyclohexane : EtOAc (gradient 50:1 to 10:1) afforded a pale yellow foam (827 mg, 72%).

LC/MS: m/z 501.9 $[M+H]^+$, $R_t$ 4.45 min.

Separation by chiral HPLC (2' x 20 cm chiralpak) eluting with heptane : EtOH (98:2), 50mL/min, wavelength 230nM afforded intermediate 33 (367 mg, $R_t$ 8.5 min) and intermediate 34 (360 mg, $R_t$ 10.0 min).

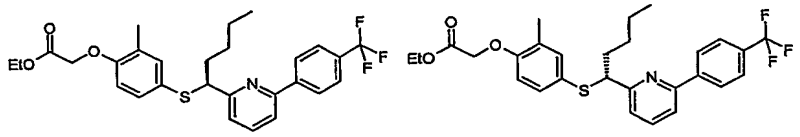
**Intermediate 35**



To a solution of intermediate 4 (1.50 g, 4.85 mmol) in dry DCM was added $SOCl_2$ (3.53 mL, 48.50 mmol), and the resulting solution stirred under nitrogen for 3 hours at rt. The mixture was then reduced under vacuum to afford intermediate 35 as an oily yellow solid (1.65 g).

LC/MS: m/z 328.2 $[M+H]^+$, $R_t$ 4.35 min.

**Intermediates 36 and 37**



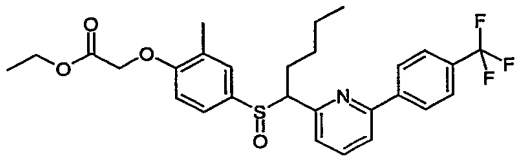
Intermediate 36 Intermediate 37

To a solution of intermediate 35 (522 mg, 1.59 mmol) in dry THF (20 mL) was added caesium carbonate (621 mg, 1.91 mmol) and ethyl (4-mercapto-2-methylphenoxy)acetate (361 mg, 1.59 mmol). The resulting mixture was stirred under nitrogen for 60 hours at rt, then at 66°C for 18 hours. The cooled reaction mixture was then diluted with water (50 mL), extracted with EtOAc (100 mL), the layers separated and the organic layer washed with brine (50 mL), dried ($Na_2SO_4$) and the solvents removed under vacuum. Purification by Biotage™ chromatography (silica, 40 g cartridge) eluting with cyclohexane : EtOAc (19:1) afforded a colourless oil (376 mg, 46%).

LC/MS: m/z 518.4 $[M+H]^+$, $R_t$ 4.51 min.

Separation of a 100 mg sample by chiral HPLC (2cm x 25cm chiralcel OJ) eluting with 5% EtOH/cycloheptane, 15ml/min, wavelength 215nm afforded intermediate 36 as a colourless oil (34 mg, $R_t$ 12.4 min) and intermediate 37 as a colourless oil (29 mg, $R_t$ 14.7 min).

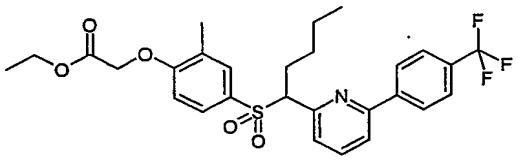
**Intermediate 38**



To a cooled (0°C, ice/water bath) solution of a racemic mixture of intermediates 36 and 37 (130 mg, 0.25 mmol) in methanol (1 mL) was added Oxone (49.5% $KHSO_5$, 204 mg, 0.33 mmol) in water (1 mL). After 15 minutes the reaction was quenched with $Na_2S_2O_5$ (237 mg, 1.24 mmol) and diluted with water (10mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10mL) and the combined organic layer washed with brine (10mL), dried ($Na_2SO_4$) and concentrated under vacuum. Purification by SPE (silica, 5 g cartridge) eluting with cyclohexane : EtOAc (gradient elution 10:1 to 2:1), afforded intermediate 38 as a mixture of isomers (60 mg, 45%).

LC/MS: m/z 534.4 $[M+H]^+$, $R_t$ 3.88 min.

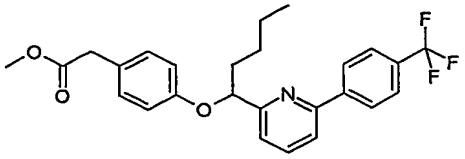
**Intermediate 39**



To a cooled 0°C (ice/water bath) solution of a racemic mixture of intermediates 36 and 37 (43 mg, 0.08 mmol) in methanol (1 mL) was added Oxone (49.5% $KHSO_5$, 153 mg, 0.25 mmol) in water (1 mL). After 4 hours 10 minutes the reaction was quenched with $Na_2S_2O_5$ (80 mg, 0.42 mmol) and diluted with water (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 x 10mL) and the combined organic layers washed with brine (30 mL), dried ($Na_2SO_4$) and concentrated under vacuum. Purification by SPE (silica, 5 g cartridge), eluting with cyclohexane : EtOAc (gradient 10:1 to 2:1) afforded intermediate 39 (26 mg, 57%).

LC/MS: m/z 550.2 $[M+H]^+$, $R_t$ 4.09 min.

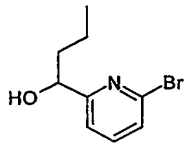
**Intermediate 40**



To a solution of intermediate 4 (349 mg, 1.13 mmol) in dry THF (22.5 mL) at 0°C (ice/water bath) under nitrogen was added methyl-4-hydroxyphenylacetate (187 mg, 1.13 mmol) followed after 1 minute by ADDM (578 mg, 2.25 mmol) in one portion. The resulting orange cloudy mixture was stirred for 3 minutes and then treated with $n$Bu$_3$P (562 µL, 2.26 mmol) drop-wise over 1 minute. The resulting pale yellow/orange mixture was then allowed to warm slowly to rt over 64 hours. The cloudy mixture was then reduced under vacuum and the residue partitioned between EtOAc (50 mL) and water (50 mL) and the layers separated. The aqueous was then re-extracted with EtOAc (50 mL) and the combined organic layer washed with brine (100 mL) dried ($MgSO_4$), filtered and reduced to give an oil which was purified by SPE (silica) eluting with cyclohexane : EtOAc (gradient 100:1 to 5:1) to give intermediate 40 (330 mg, 64%).

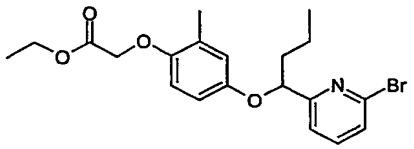
LC/MS: m/z 457.9 $[M+H]^+$, $R_t$ 4.32 min.

**Intermediate 41**




A solution of 2,6-dibromopyridine (1.00 g, 4.22 mmol) in THF (40 mL) was cooled to -78°C (dry-ice/acetone bath) and treated with $n$BuLi (2.64 mL of a 1.6M solution in hexanes, 4.22 mmol) drop-wise over 10 minutes under nitrogen. After 30 minutes at this temperature the pale yellow/green solution was treated with butyraldehyde (400 µL, 4.44mmol) drop-wise over 5 minutes and the resulting orange/red solution stirred at this temperature for 1 hour. The solution was then allowed to warm slowly to 0°C (ice/water bath) over 20 minutes and was then quenched by the drop-wise addition of aqueous HCl (2M, 4 mL). The resulting pale yellow solution was reduced to an oil, partitioned between EtOAc (100 mL) and aqueous HCl (2M, 100 mL), and the layers separated. The aqueous was re-extracted with EtOAc (100 mL) and the combined organic layer washed with water (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and reduced to an orange/yellow oil. Purification by SPE (silica) eluting with cyclohexane : EtOAc (gradient 100:1 to 2:1) afforded intermediate 41 (626 mg, 64%).

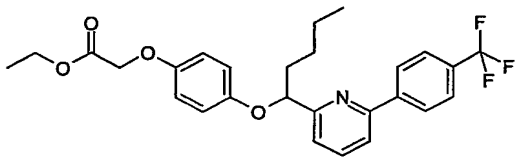
**Intermediate 42**



To a stirred solution of intermediate 41 (626 mg, 2.72 mmol) and ethyl (4-hydroxy-2-methylphenoxy)acetate (539 mg, 2.56 mmol) in dry THF (51 mL) at 0°C (ice/water bath) under nitrogen was added ADDM (1.32 g, 5.13 mmol) followed by $n$Bu$_3$P (1.28 mL, 4.95 mmol) drop-wise. The mixture was stirred with slow warming to rt over 18 hours and then concentrated under vacuum, diluted with EtOAc (150 mL) and washed with water (3 x 75 mL), dried ($Na_2SO_4$), filtered and reduced to give a yellow oil. Purification by SPE (silica, 20 g cartridge) eluting with cyclohexane : EtOAc (gradient 20:1 to 10:1) afforded intermediate 42 (388 mg, 34%).

LC/MS: m/z 423.8 $[M+H]^+$, $R_t$ 3.92 min.

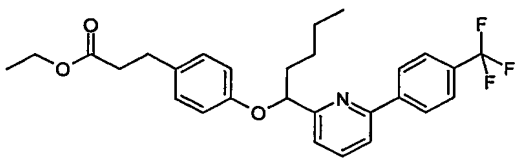
**Intermediate 43**



To a solution of intermediate 4 (99 mg, 0.32 mmol) in dry THF (6.4 mL) at 0°C (ice/water bath) under nitrogen was added ethyl (4-hydroxyphenoxy)acetate (63 mg, 0.32 mmol) followed after 1 minute by ADDM (164 mg, 0.64 mmol) in one portion. The resulting orange slurry was stirred for 2 minutes and then treated with $n$Bu$_3$P (159 µL, 0.64 mmol) drop-wise over 1 minute. The resulting pale yellow/orange mixture was then allowed to warm slowly to rt over 69 hours. The cloudy mixture was then reduced under vacuum and the residue purified by SPE (silica) eluting with cyclohexane : EtOAc (gradient 100:1 to 1:1) to give intermediate 43 (42 mg, 27%).

LC/MS: m/z 487.9 $[M+H]^+$, $R_t$ 4.33min.

**Intermediate 44**

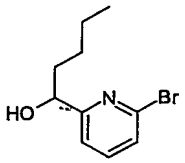


To a stirred solution of the intermediate 4 (50 mg, 0.16 mmol) and ethyl 3-(4-hydroxyphenyl)propanoate (31 mg, 0.16 mmol) in anhydrous THF (3.2 mL) under nitrogen at 0°C (ice/water bath) was added ADDM (83 mg, 0.32 mmol). After a few minutes, $n$Bu$_3$P (81 µL, 0.32

mmol) was added (drop-wise) and the solution was stirred at 0°C warming to rt overnight. After 17.5 hours the solvent was concentrated under vacuum and the solid residue dissolved in DCM (5 mL) and washed with water (5 mL) using a hydrophobic frit. The aqueous layer was re-extracted with DCM (5 mL) and the combined organic layers concentrated under vacuum. The resulting solid residue was then purified by SPE (silica, 5 g cartridge) eluting with cyclohexane : EtOAc (gradient 100:1 to 1:1) to afford intermediate 44 (29 mg, 37%).

LC/MS: m/z 486.1 $[M+H]^+$, $R_t$ 4.33 min.

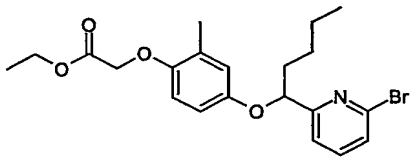
**Intermediate 45**




To a solution of *n*BuLi (26.40 mL of a 1.6M solution in hexanes, 42.24 mmol) in THF (25 mL) at -78°C (dry-ice/acetone bath) was added a solution 2,6-dibromopyridine (10.00 g, 42.21 mmol) in THF (60 mL) drop-wise over 45 minutes under nitrogen. The resulting dark green coloured solution was stirred at -78°C for 15 minutes and then valeraldehyde (6.70 mL, 63.01 mmol) was added drop-wise over 1 minute. The resulting dark purple coloured solution was stirred at -78°C for 15 minutes and was then treated in one portion with a mixture of methanol (42 mL) and AcOH (2.70 mL, 47.16 mmol). The resulting pale yellow coloured solution was then allowed to warm to rt slowly over 1 hour. The mixture was then diluted with saturated aqueous $NH_4Cl$ (200 mL) and the product extracted with EtOAc (2 x 200 mL). The combined organic layer was then washed with brine (250 mL), dried ($MgSO_4$), filtered and reduced to an orange oil (10.31g, 100%). Purification of 7.14 g of this material by Biotage™ chromatography (silica) eluting with cyclohexane : EtOAc (gradient 100:1 to 1:1) afforded intermediate 45 as a clear, pale yellow oil (4.48 g, 63%).

LC/MS: m/z 246.0 $[M+H]^+$, $R_t$ 3.03 min.

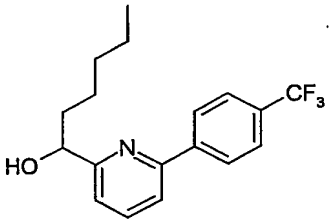
**Intermediate 46**



To a stirred solution of intermediate 45 (525 mg, 2.15 mmol) and ethyl (4-hydroxy-2-methylphenoxy)acetate (452 mg, 2.15 mmol) in dry THF (43 mL) at 0°C (ice/water bath) under nitrogen was added ADDP (1.09 g, 4.32 mmol) followed by $n$Bu$_3$P (1.07 mL, 4.30 mmol) dropwise. The mixture was stirred with slow warming to rt over 72 hours and then concentrated under vacuum, diluted with EtOAc (200 mL) and washed with water (3 x 200 mL), brine (200 mL), dried ($MgSO_4$), filtered and reduced to give a yellow oil. Purification by SPE (silica, 20 g Cartridge) eluting with cyclohexane : EtOAc (gradient 20:1 to 10:1) afforded intermediate 46 (478 mg, 51%).

LC/MS: m/z 438.0 $[M+H]^+$, $R_t$ 3.92 min.

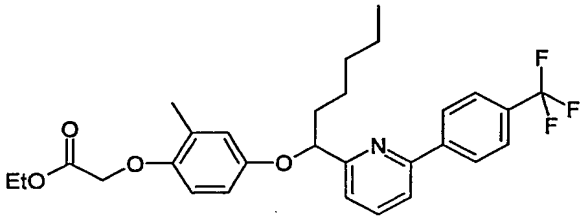
**Intermediate 47**



A solution of intermediate 5 (300 mg, 1.19 mmol) in dry toluene (12 mL) under nitrogen was cooled to 0°C (ice/water bath) and treated with $n$-pentylmagnesium bromide (0.66 mL of a 2M solution in $Et_2O$, 1.31 mmol) and the resulting mixture was stirred at 0°C for 2 hours. The reaction was then quenched by the cautious addition of aqueous HCl (2M, 2 mL) and the solvent was removed under vacuum and the residue partitioned between EtOAc (2 x 50 mL) and aqueous HCl (2M, 50 mL). The organic solution was washed with water (60 mL) then brine (60 mL), dried ($MgSO_4$) and reduced. Purification by SPE (silica, 20g cartridge) eluting with cyclohexane : EtOAc (gradient 99:1 to 19:1) afforded intermediate 47 as a colourless oil (131 mg, 34%).

LC/MS: m/z 324.1$[M+H]^+$, $R_t$ 3.88 min.

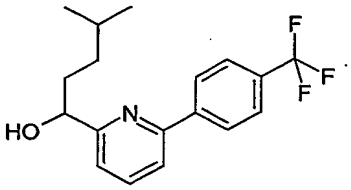
**Intermediate 48**



A solution of intermediate 47 (131 mg, 0.41 mmol) in dry THF (15 mL) under nitrogen was cooled to 0°C and treated with ethyl (4-hydroxy-2-methylphenoxy)acetate (85 mg, 0.41 mmol), ADDM (210 mg, 0.82 mmol) and $n$Bu$_3$P (204 µL, 0.82 mmol). The reaction mixture was then allowed to warm to rt slowly over 22 hours. The solvent was removed under vacuum and the residue partitioned between EtOAc (2 x 30 mL) and water (30 mL). The layers were separated and the organic layer dried ($Na_2SO_4$) and reduced. Purification by SPE (silica, 20 g cartridge) eluting with cyclohexane : EtOAc (49:1 to 24:1) afforded intermediate 48 as a colourless oil (80 mg, 38%).

LC/MS: m/z 516.1 $[M+H]^+$, $R_t$ 4.37 min.

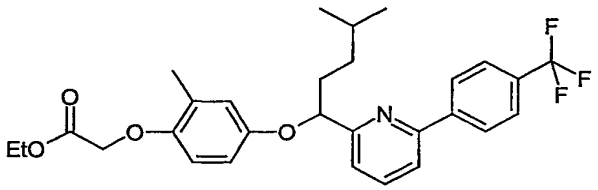
**Intermediate 49**



A solution of intermediate 5 (350 mg, 1.39 mmol) in $Et_2O$ (14 mL) was cooled to 0°C. To this was slowly added the freshly prepared Grignard reagent (1.26 mL, 1.53 mmol), prepared from magnesium turnings (500 mg, 0.02 mol) and 1-bromo-3-methyl butane (2.34 mL, 0.02 mol) in dry $Et_2O$ (16.5 mL). The resulting mixture was stirred under nitrogen at 0°C. After 1.5 hours, more Grignard reagent (0.3 mL, 0.36 mmol) was added and the resulting mixture stirred at 0°C for a further 1.5 hours. The reaction mixture was then quenched by cautious addition of aqueous HCl (2M, 3 mL) and the solvent removed under vacuum. The residue was partitioned between EtOAc (30 mL) and water (20 mL), the layers separated and the aqueous re-extracted with EtOAc (30 mL). The combined organic layer was washed with brine (50 mL), dried ($MgSO_4$) and reduced under vacuum. Purification by SPE (silica, 20 g cartridge), eluting with cyclohexane : EtOAc (gradient 99:1 to 1:1) followed by EtOAc then MeOH afforded intermediate 49 as a colourless oil (179 mg, 40%).

LC/MS: m/z 324.1 $[M+H]^+$, $R_t$ 3.8 min.

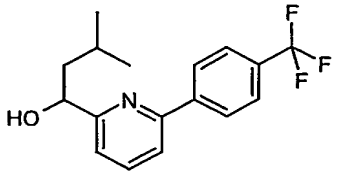
**Intermediate 50**



Prepared from intermediate 49 (80 mg, 0.25 mmol) according to the procedure used for the preparation of intermediate 48 to give, after purification by SPE (silica, 10 g cartridge) eluting with cyclohexane : EtOAc (gradient 99:1 to 1:1) afforded the intermediate 50 as a colourless oil (13.2 mg, 10%).

LCMS: m/z 516.2 $[M+H]^+$, $R_t$ 4.42 min.

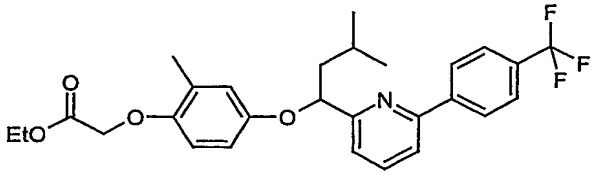
**Intermediate 51**



Prepared from intermediate 5 (500 mg, 1.99 mmol) in $Et_2O$ (20 mL) and isobutylmagnesium bromide (1.1 mL of a 2M solution in $Et_2O$, 2.2 mmol) according to the procedure used for the preparation of intermediate 47 to give, after purification by SPE (silica, 10 g cartridge) eluting with cyclohexane : EtOAc (gradient 99:1 to 4:1) intermediate 51 as a white crystalline solid (215 mg, 35%).

LC/MS: m/z 310.1 $[M+H]^+$, $R_t$ 3.74 min.

**Intermediate 52**

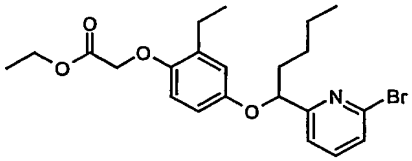


A solution of intermediate 51 (180 mg, 0.58 mmol) in dry THF (12 mL) under nitrogen was treated with ethyl (4-hydroxy-2-methylphenoxy)acetate(122 mg, 0.58 mmol) and cooled to 0°C. This was treated portion-wise with ADDP (0.3 g, 1.2 mmol), then drop-wise with $n$Bu$_3$P (0.29 mL, 1.2 mmol). The resulting pale yellow suspension allowed to warm to rt slowly over 16 hours. The

solvent was removed under vacuum and the residue partitioned between EtOAc (60 mL) and water (60 mL) and the layers separated. The aqueous was re-extracted with EtOAc (60 mL) and the combined organic layer dried ($Na_2SO_4$) and reduced. Purification by SPE (silica, 10 g cartridge) eluting with cyclohexane : EtOAc (gradient 99:1 to 49:1) gave intermediate 52 as a colourless oil (137 mg, 47%).

LC/MS: m/z 502.1 $[M+H]^+$, $R_t$ 4.31 min.

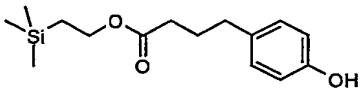
**Intermediate 53**



To a stirred solution of intermediate 45 (250 mg, 1.02 mmol) and ethyl (4-hydroxy-2-ethylphenoxy)acetate (230 mg, 1.02 mmol) in dry THF (21 mL) at 0°C (ice/water bath) under nitrogen was added ADDP (517 mg, 2.04 mmol) followed by $n$Bu$_3$P (510 µL, 2.04 mmol) drop-wise. The mixture was stirred with slow warming to rt over 18 hours and then concentrated under vacuum, diluted with EtOAc (150 mL) and washed with water (3 x 75 mL), dried ($MgSO_4$), filtered and reduced to give an oil. Purification by SPE (silica, 10 g Cartridge) eluting with cyclohexane : EtOAc (gradient 20:1 to 5:1) afforded intermediate 53 (307 mg, 67%).

LC/MS: m/z 452.0 $[M+H]^+$, $R_t$ 4.03 min.

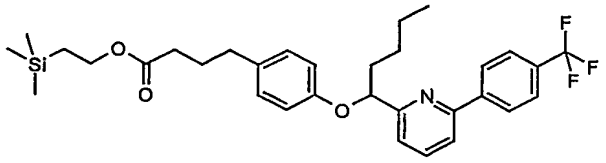
**Intermediate 54**



To a stirred solution of 2-(trimethylsilyl) ethanol (0.56 mL, 3.91 mmol) in THF (1 mL) at rt under nitrogen, was added 4-DMAP (113 mg, 0.92 mmol) followed by EDC (177 mg, 0.92 mmol). After about 1 minute $Et_3N$ (170 µL, 1.22 mmol) was added, drop-wise followed by 4-(4-hydroxyphenyl)butanoic acid (150 mg, 0.83 mmol) in THF (4 mL) and the mixture stirred at rt for 18 hours. The mixture was then partitioned between $Et_2O$ (25 mL) and aqueous HCl (2M, 30 mL) and the layers separated. The aqueous layer was re-extracted with $Et_2O$ (20 mL) and the combined organic layer washed with brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum to give a 'chalk-white' milky oil. Purification by SPE (silica, 5 g Cartridge) eluting with cyclohexane : EtOAc (gradient 25:1 to 1:2) afforded intermediate 54 (55mg).

LC/MS: m/z 298.2 $[M+NH_4]^+$, $R_t$ 3.63 min.

**Intermediate 55**

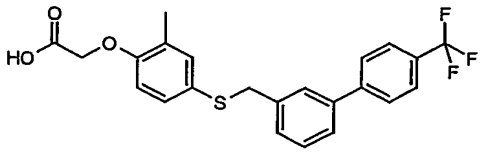


To a stirred solution of intermediate 4 (62 mg, 0.20 mmol) and intermediate 54 (55 mg, 0.20 mmol) in dry THF (4 mL) at 0°C (ice/water bath), under nitrogen, was added ADDP (102 mg, 0.40 mmol) followed by $n$Bu$_3$P (100 □L, 0.40 mmol), and the mixture stirred with slow warming to rt over 64.5 hours. The mixture was then concentrated under vacuum and the solid residue partitioned between DCM (5 mL) and water (5 mL) using a hydrophobic frit. The layers were separated and the aqueous layer re-extracted with DCM (5 mL) and the combined organic layer reduced. Purification by SPE (silica, 5 g Cartridge) eluting with cyclohexane : EtOAc (gradient 50:1 to 7.5:1) afforded intermediate 55 (42 mg).

LC/MS: m/z 572.2 $[M+H]^+$, $R_t$ 4.75 min.

**Example 1**

**[2-Methyl-4-({[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methyl}thio)phenoxy]acetic acid**



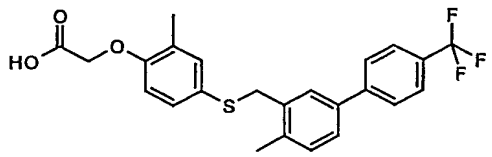
A solution of intermediate 8 in THF (20 mL) and aqueous NaOH (2M, 20 mL) was stirred at rt overnight and then heated to 60°C for 2 hours. The mixture was then allowed to cool to rt and the THF removed under vacuum. The resulting aqueous mixture was then acidified and extracted with EtOAc (3 x) and the organic layer washed with brine dried ($MgSO_4$), filtered and reduced. Purification by mass directed auto-prep HPLC afforded the title compound as a white solid.

LC/MS: m/z 431.0 $[M-H]^+$, $R_t$ 4.80 min.

$^1$H NMR (400MHz; $CDCl_3$) δ: 2.22 (3H, s), 4.06 (2H, s), 4.66 (2H, s), 6.63 (1H, d, J 8.5 Hz), 7.14 (1H, dd, J 8.5, 2.5 Hz), 7.16, (1H, m), 7.24-7.28 (1H, m), 7.34-7.41 (2H, m), 7.46 (1H, m), 7.60 (2H, d, J 8.0 Hz), 7.67 (2H, d, J 8.0 Hz).

**Example 2**

**[2-Methyl-4-({[4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methyl}thio)phenoxy]acetic acid**



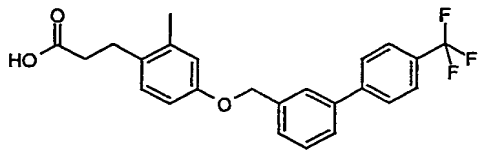
A mixture of intermediate 9 (90 mg, 0.45 mmol), 4-(triflouromethyl)benzeneboronic (94 mg, 0.49 mmol), $Pd(PPh_3)_4$ (5 mg, 0.004 mmol) and $Na_2CO_3$ (123 mg, 1.16 mmol) in a mixture of DME (20 mL) and water (10 mL) was heated at reflux for 7 hours and then allowed to cool to rt. The resulting mixture was then reduced under vacuum, partitioned between water and EtOAc and the layers separated. The organic layer was then washed with brine, reduced under vacuum and then purified by SPE (silica, 10g cartridge) eluting with cyclohexane : $CHCl_3$ then cyclohexane : EtOAc to give a crude product containing a mixture of intermediate 9 and product. The mixture was then dissolved in DCM (10 mL) and then treated with thionyl chloride (200 µL, 2.74 mmol) and the mixture stirred for 5 hours. Additional thionyl chloride (200 µL, 2.74 mmol) was then added and after a further 2 hours, the reaction was quenched by the careful addition of aqueous $K_2CO_3$ (1N) and the resulting layers separated using a hydrophobic frit. The organic layer was reduced and the resulting crude mixture (98 mg) dissolved in MeCN (20 mL) was and treated ethyl (4-mercapto-2-methylphenoxy)acetate (92 mg, 0.41 mmol) and $K_2CO_3$ (55 mg, 0.40 mmol). The resulting mixture was then stirred under nitrogen over the 72 hours and the resulting mixture partitioned between water and EtOAc and the layers separated. The aqueous was re-extracted with EtOAc and the combined organic layers washed with brine, dried ($MgSO_4$), filtered and reduced. Purification by SPE (silica) eluting with cyclohexane : $CHCl_3$ (1:1) afforded the crude ester as a clear oil (125 mg). A solution of the ester in THF (10 mL) and aqueous NaOH (2M, 10 mL) was heated at 60°C for 1 hour and was then allowed to cool to rt overnight. The THF was then removed under vacuum and the resulting aqueous mixture was then acidified and extracted with EtOAc (2 x). The organic layer was then washed with brine, dried ($MgSO_4$), filtered and reduced. Purification by mass directed auto-prep HPLC afforded the title compound (41 mg) as a white solid.

LC/MS: m/z 445.0 $[M-H]^+$, $R_t$ 4.32 min.

$^1H$ NMR (400MHz; DMSO-$d^6$) δ: 2.07 (3H, s), 2.35 (3H, s), 4.10 (2H, s), 4.64 (2H, s), 6.74 (1H, d, J 8.5 Hz), 7.09 (1H, m), 7.14 (1H, dd, J 8.0, 2.5 Hz), 7.24-7.30 (2H, m), 7.46 (1H, dd, J 8.0, 2.0 Hz), 7.64 (2H, d, J 8.5 Hz), 7.67 (2H, d, J 8.5 Hz).

**Example 3**

**3-(2-Methyl-4-{[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]methoxy}phenyl)propanoic acid**



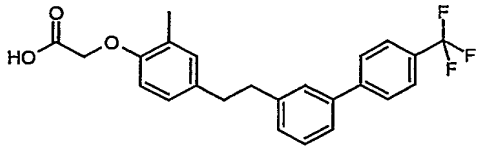
A solution of intermediate 10 (135 mg, 0.31 mmol) in THF (4 mL) at rt was treated with aqueous NaOH (2M, 4 mL) and the resulting solution heated to 75°C for 7 hours and then allowed to cool to rt over 21 hours. The mixture was then reduced and the residue partitioned between $CHCl_3$ and water and the aqueous phase separated and acidified to pH2 with aqueous HCl (2 N). The mixture was then extracted with $CHCl_3$ (3 x) and the combined organic layer washed with brine, dried ($Na_2SO_4$), filtered and reduced to give the title compound as a white crystalline solid (123 mg, 97%).

LC/MS: m/z 413.1 $[M-H]^+$, $R_t$ 4.21 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 2.31 (3H, s), 2.62 (2H, m), 2.91 (2H, m), 5.10 (2H, s), 6.79 (1H, dd, J 8.5, 3.0 Hz), 6.83 (1H, d, 3.0 Hz), 7.08 (1H, d, J 8.5 Hz), 7.44-7.53 (2H, m), 7.56 (1H, m), 7.66 (1H, m), 7.70 (4H, s).

**Example 4**

**(2-Methyl-4-{2-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]ethyl}phenoxy)acetic acid**



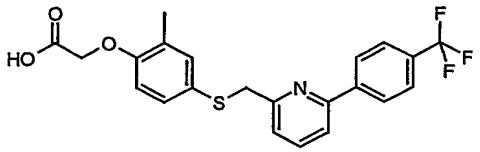
A suspension of intermediate 12 (90 mg, 0.22 mmol) in EtOH (10 mL) was added to Pd/C (Degussa type E101 NE/N) (10 mg, 11wt%) and the resulting mixture stirred under an atmosphere of hydrogen for 6 hours. The mixture was then filtered through celite J2 washing with copious amounts of EtOH and the filtrate reduced under vacuum to give a sticky solid (100 mg) which was purified by mass directed auto-prep HPLC to give the title compound as a fluffy white solid.

LC/MS: m/z 413.1 $[M-H]^+$, $R_t$ 4.48 min.

$^1H$ NMR (400MHz; MeOD-$d^4$) δ2.21 (3H, s), 2.85 (2H, m), 2.95 (2H, m), 4.62 (2H, s), 6.70 (1H, d, J 8.0 Hz), 6.91-6.95 (2H, m), 7.22 (1H, dt, J 7.5,1.0 Hz), 7.35 (1H, m), 7.37 (1H, t, J 7.5 Hz), 7.46 (1H, ddd, J 7.5, 2.0, 1.0 Hz), 7.72 (4H, s).

**Example 5**

**{2-Methyl-4-[({6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}methyl)thio]phenoxy}acetic acid**



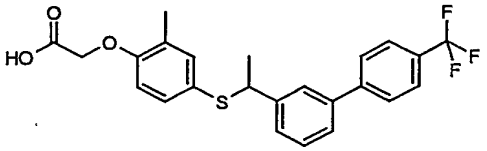
A solution of intermediate 13 (367 mg, 0.80 mmol) in THF (5 mL) was treated with aqueous NaOH (2M, 5 mL) and the resulting solution stirred at rt for 4 hours. The mixture was poured into a mixture of aqueous HCl (2M) and EtOAc and the layers separated. The organic layer was then washed with water and brine, dried $MgSO_4$, filtered and then reduced under vacuum. Purification by mass-directed auto-prep HPLC afforded the title compound as an oil.

LC/MS: m/z 434.2 $[M+H]^+$, $R_t$ 3.97 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 2.22 (3H, s), 4.24 (2H, s), 4.63 (2H, s), 6.61 (1H, d, J 8.5 Hz), 7.16 (1H, dd, J 8.5, 2.0 Hz), 7.22-7.28 (2H, m), 7.60 (1H, d, J 8.5 Hz), 7.68-7.74 (3H, m), 8.02 (2H, d, J 8.0 Hz).

**Example 6**

**[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]ethyl}thio)phenoxy]acetic acid**



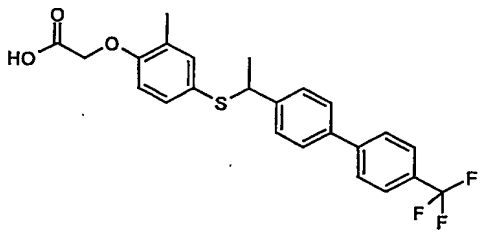
A mixture of intermediate 16 (235 mg, 0.50 mmol) in dioxane (6 mL) was treated with aqueous NaOH (0.5N, 2.0 mL, 1.00 mmol) and the mixture heated at reflux for 1 hour. The resulting mixture was then cooled and treated with Dowex 50WX2 (pre-washed with dioxan), filtered and washed with more dioxan and reduced to give the title compound as a colourless gum (220 mg, 99%).

LC/MS: m/z 445.2 $[M-H]^+$, $R_t$ 4.20 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 1.65 (3H, d, J 7.0 Hz), 2.18 (3H, s), 4.25 (1H, q, J 7.0 Hz), 4.64 (2H, s), 6.57 (1H, d, J 9.0 Hz), 7.08-7.13 (2H, m), 7.29 (1H, m), 7.33-7.41 (2H, m), 7.43 (1H, m), 7.59 (2H, d, J 8.5 Hz), 7.67 (2H, m, J 8.5 Hz).

**Example 7**

**[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]ethyl}thio)phenoxy]acetic acid**



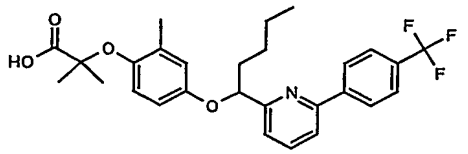
Prepared from intermediate 19 (333 mg, 0.70 mmol) according to the procedure used for the preparation of example 6 to give the title compound as a white solid (283 mg, 90%).

LC/MS: m/z 445.2 $[M-H]^+$, $R_t$ 4.28 min.

$^1$H NMR (400MHz; $CDCl_3$) δ: 1.63 (3H, d, J 7.0 Hz), 2.19 (3H, s), 4.24 (1H, q, J 7.0 Hz), 4.65 (2H, s), 6.58 (1H, d, J 8.5 Hz), 7.08-7.14 (2H, m), 7.33 (2H, d, J 8.5 Hz), 7.50 (2H, d, J 8.5 Hz), 7.67 (4H, m).

**Example 8**

**2-Methyl-2-{2-methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}propanoic acid**



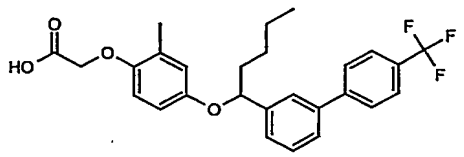
Intermediate 20 (9 mg, 0.02 mmol) was dissolved in THF (0.75 mL), water (0.25 mL) and aqueous NaOH (2M, 35 µl, 0.07 mmol) and the mixture heated at 80°C for 16 hours. More aqueous NaOH (2M, 420 µl, 0.84 mmol) was then added and heating continued for an additional 24 hours. The mixture was then cooled, neutralised with aqueous HCl (2M), partitioned between EtOAc and water and the layers separated. The organic layer was then washed with brine, dried ($Na_2SO_4$) and reduced to give a pale yellow oil. Purification by SPE (aminopropyl, 1g cartridge) loading in $CHCl_3$ and eluting with dioxane and then 10% aqueous ammonia in dioxane afforded the title compound as a colourless gum (4.5 mg, 53%).

LC/MS: m/z 502.3 $[M+H]^+$, $R_t$ 4.49.

$^1$H NMR (400MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.50 (6H, s), 1.32-1.61 (4H, m), 2.00 (2H, m), 2.15 (3H, s), 5.23 (1H, t, J 6.0 Hz), 6.57 (1H, dd, J 8.5, 3.0 Hz), 6.69 (1H, d, J 8.5 Hz), 6.76 (1H, d, J 3.0 Hz), 7.37 (1H, dd, J 8.0, 1.0 Hz), 7.62 (1H, dd, J 8.0, 1.0 Hz), 7.73 (1H, t, J 8.0 Hz), 7.74 (2H, d, J 8.0 Hz), 8.12 (2H, d, J 8.0 Hz).

**Example 9**

**[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-3-yl]pentyl}oxy)phenoxy]acetic acid**



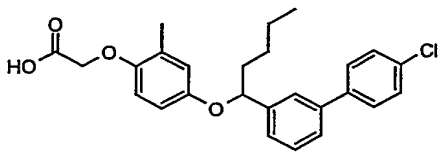
Intermediate 23 (138 mg, 0.28 mmol) was dissolved in THF (1.5 mL), water (0.5 mL) and aqueous NaOH (2M, 0.52 mL, 1.04 mmol) and the mixture stirred at 70°C for 2 hours, cooled to rt and acidified to pH4 with aqueous hydrochloric acid (2M). The mixture was then partitioned between EtOAc and water, the layers separated and the organic layer washed with brine, dried ($Na_2SO_4$) and concentrated to give the title compound as a colourless gum (130 mg, 100%).

LC/MS: m/z 471.2 $[M-H]^+$, $R_t$ 4.57 min.

$^1$H NMR (400MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.0 Hz), 1.31-1.45 (3H, m), 1.45-1.60 (1H, m), 1.76-1.90 (1H, m), 1.93-2.07 (1H, m), 2.20 (3H, s), 4.55 (2H, s), 5.03 (2H, dd, J 8.0, 5.0 Hz), 6.55 (1H, d, J 9.0 Hz), 6.58 (1H, dd, J 9.0, 2.5 Hz), 6.75 (1H, 2.5 Hz), 7.36 (1H, m), 7.42 (1H, t, J 7.5 Hz), 7.48 (1H, dt, J 7.5, 1.5 Hz), 7.5 (1H, m), 7.67 (4H, m).

**Example 10**

**(4-{[1-(4'-Chloro-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid**



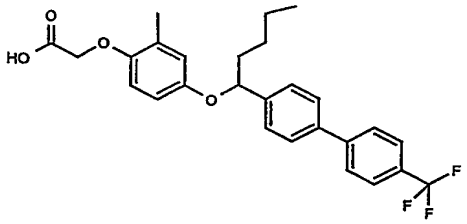
Prepared according to the procedure used for the preparation of example 9 starting from intermediate 24 (137 mg, 0.29 mmol) to give the title compound (130 mg, 100%).

LC/MS m/z 456.1 $[M+NH_4]^+$, $R_t$ 4.55min.

$^1$H NMR (400MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.0 Hz), 1.30-1.44 (3H, m), 1.44-1.59 (1H, m), 1.76-1.88 (1H, m), 1.94-2.06 (1H, m), 2.21 (3H, s), 4.51 (2H, s), 5.02 (2H, dd, J 8.0, 5.0 Hz), 6.53 (1H, d, J 9.0 Hz), 6.56 (1H, dd, J 9.0, 2.5 Hz), 6.74 (1H, 2.5 Hz), 7.32 (1H, dt, J 7.5, 1.5 Hz), 7.36-7.41 (3H,m), 7.43 (1H, dt, J 7.5, 1.5 Hz), 7.47-7.53 (4H, m).

**Example 11**

**[2-Methyl-4-({1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}oxy)phenoxy]acetic acid**



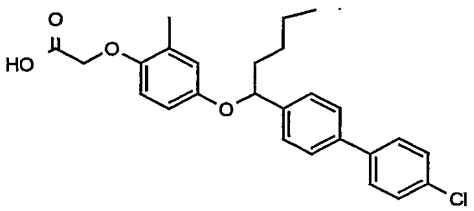
To a solution of intermediate 27 (310 mg, 0.62 mmol) in dioxan (6 mL) and water (3 mL), was added aqueous NaOH (2M, 2.43 mL, 1.22 mmol), and the mixture stirred at rt for 1 hour. The dioxan was removed under vacuum and brine (5 mL) added to the residue. The precipitate was collected by filtration and dried under vacuum to give the title compound as a white solid (250 mg, 85%).

LC/MS: m/z 471.3 $[M-H]^+$, $R_t$ 4.57 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.91 (3H, t, J 7.0 Hz), 1.37 (2H, m), 1.39 (1H, m), 1.49 (1H, m), 1.80 (1H, m), 1.95 (1H, m), 2.17 (3H, s), 4.26 (2H, s), 5.11 (1H, dd, J 5.5, 5.5 Hz), 6.55 (1H, dd, J 8.5, 2.0 Hz), 6.58 (1H, d, J 8.5 Hz), 6.68 (1H, d, J 2.0 Hz), 7.44 (2H, d, J 8.0 Hz), 7.61 (2H, d, J 8.0 Hz), 7.70 (2H, d, J 8.0 Hz), 7.77 (2H,d, J 8.0 Hz).

**Example 12**

**(4-{[1-(4'-Chloro-1,1'-biphenyl-4-yl)pentyl]oxy}-2-methylphenoxy)acetic acid**



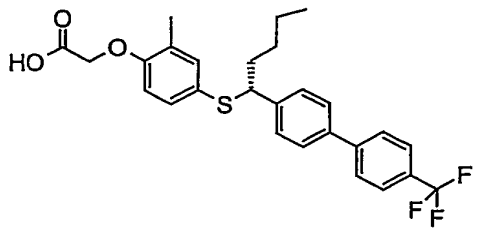
Prepared from intermediate 29 (150 mg, 0.32 mmol) according to the procedure used for the preparation of example 11, to give the title compound as a white solid (140 mg, 99%).

LC/MS: m/z 437.2 $[M-H]^+$, $R_t$ 4.83 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.90 (3H, t, J 7.0 Hz), 1.36 (2H,m), 1.39 (1H, m), 1.49 (1H, m), 1.80 (1H, m), 1.95 (1H, m), 2.16 (3H, s), 4.26 (2H, s), 5.11 (1H, dd, J 7.5, 5.5 Hz), 6.54 (1H, dd, J 9.0, 2.5 Hz), 6.58 (1H, d, J 9.0 Hz), 6.68 (1H, d, J 2.5 Hz), 7.39 (4H, d, J 8.5Hz), 7.53 (2H, d, J 8.5 Hz), 7.57(2H, d, J 8.5 Hz).

**Example 13**

**[2-Methyl-4-({(1R)-1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}thio)phenoxy]acetic acid**



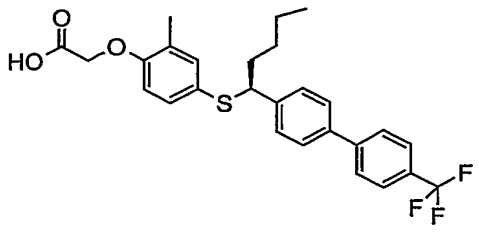
To a solution of intermediate 31 (10 mg, 0.02 mmol) in THF (1 mL) and MeOH (1 mL) was added aqueous NaOH (2M, 1 mL) and the resulting mixture agitated for 1.5 hours at rt. The mixture was then reduced under vacuum, acidified with aqueous HCl (2M), extracted with DCM (2 mL) and reduced to afford the title compound as colourless oil (9 mg, 95%).

LC/MS: m/z 487.3 $[M-H]^+$ $R_t$ 4.84 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.85 (3H, t, J 7.0 Hz), 1.21-1.44 (4H, m), 1.84-2.02 (2H, m), 2.12 (3H, s), 4.06 (1H, dd, J 8.5, 6.5 Hz), 4.62 (2H, s), 6.64 (1H, d, J 8.5 Hz), 7.01 (1H, d, J 2.0 Hz), 7.04 (1H, dd, J 8.5, 2.0 Hz), 7.26 (2H, d, J 8.0 Hz), 7.55 (2H, d, J 8.0 Hz), 7.70 (2H, d, J 8.0 Hz), 7.77 (2H, d, J 8.0 Hz).

**Example 14**

**[2-Methyl-4-({(1S)-1-[4'-(trifluoromethyl)-1,1'-biphenyl-4-yl]pentyl}thio)phenoxy]acetic acid**



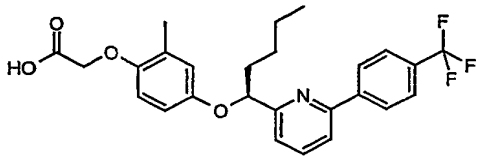
Prepared from intermediate 32 (9 mg, 0.02 mmol) according to the procedure used for the preparation of example 13 to give the title compound (8 mg, 94%).

LC/MS: m/z 487.3 $[M-H]^+$ $R_t$ 4.84 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.85 (3H, t, J 7.0 Hz), 1.21-1.44 (4H, m), 1.84-2.02 (2H, m), 2.12 (3H, s), 4.06 (1H, dd, J 8.5, 6.5 Hz), 4.62 (2H, s), 6.64 (1H, d, J 8.5 Hz), 7.01 (1H, d, J 2.0 Hz), 7.04 (1H, dd, J 8.5, 2.0 Hz), 7.26 (2H, d, J 8.0 Hz), 7.55 (2H, d, J 8.0 Hz), 7.70 (2H, d, J 8.0 Hz), 7.77 (2H, d, J 8.0 Hz).

**Example 15**

**{2-Methyl-4-[((1S)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid**



A solution of intermediate 33 (367 mg, 0.73 mmol) in THF (9 mL) and methanol (9 mL) was treated with aqueous NaOH (2M, 9 mL) drop-wise and the resulting solution stirred at rt for 3 h. The volatile solvents were then removed under vacuum and the resulting aqueous residue diluted with water (100 mL) and then acidified with aqueous HCl (2M, 11 mL). The product was extracted with DCM (2 x 50 mL). The combined organic layers were then washed with brine (150 mL), dried ($MgSO_4$), filtered and then reduced under vacuum to give a pale yellow foam (341 mg). Purification by SPE (silica) eluting with heptane : EtOAc (gradient 10:1 to 0:1) afforded the title compound as a pale yellow foam (256 mg, 74%).

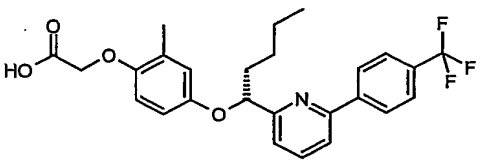
LC/MS: m/z 473.9 $[M+H]^+$, $R_t$ 4.38 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.63 (4H, m), 2.00 (2H, m), 4.55 (2H, s), 5.22 (1H, m), 6.53-6.63 (2H, m), 6.79 (1H, d, J 2.0 Hz), 7.37 (1H, d, J 8.0 Hz), 7.62 (1H, d, J 8.0 Hz), 7.73 (3H, m), 8.13 (2H, d, J 8.0 Hz).

Analytical chiral HPLC, 25cm chiralpak AD, 5% EtOH/cycloheptane [0.1%TFA], 1.0 mL/min, wavelength 215 nm, $R_t$ 9.53 min.

**Example 16**

**{2-Methyl-4-[((1R)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid**



Prepared from intermediate 34 (360 mg, 0.72 mmol) according to the procedure used for the preparation of example 15 to give the title compound as a pale yellow foam (269 mg, 79%).

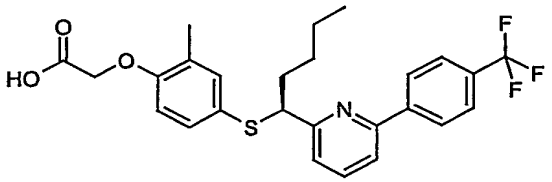
LC/MS: m/z 473.9 $[M+H]^+$, $R_t$ 4.38 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.63 (4H, m), 2.00 (2H, m), 4.55 (2H, s), 5.22 (1H, m), 6.53-6.63 (2H, m), 6.79 (1H, d, J 2.0 Hz), 7.37 (1H, d, J 8.0 Hz), 7.62 (1H, d, J 8.0 Hz), 7.73 (3H, m), 8.13 (2H, d, J 8.0 Hz).

Analytical chiral HPLC 25cm chiralpak AD 5% EtOH/heptane [0.1%TFA], 1.0 mL/min, wavelength 215 nm, $R_t$ 10.87 min

**Example 17**

**{2-Methyl-4-[((1S)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)thio]phenoxy}acetic acid**



To a solution of intermediate 36 (34 mg, 0.07 mmol) in THF (1 mL) and MeOH (1 mL) was added aqueous NaOH (2M, 1 mL) and the resulting mixture agitated for 1.5 hours at rt. The mixture was then reduced under vacuum, acidified with aqueous HCl (2M) and extracted with DCM (2 mL) and reduced to afford the title compound as a colourless oil (31 mg).

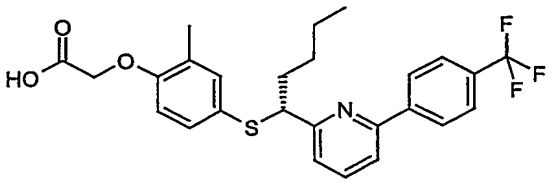
LC/MS: m/z 490.0 $[M+H]^+$ $R_t$ 4.60 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.86 (3H, t, 7.0 Hz), 1.23-1.48 (4H, m), 1.95-2.18 (2H, m), 2.08 (3H, s) 4.23 (1H, dd, J 8.5, 6.5 Hz), 4.54 (2H, s), 6.62 (1H, d, J 8.5 Hz), 6.97 (1H, d, J 1.5 Hz), 7.04 (1H, dd, J 8.5 Hz, 1.5 Hz), 7.26 (1H, d, J 8.0 Hz), 7.70 (1H, d, J 8.0 Hz), 7.73 (2H, d, J 8.0 Hz), 7.77 (1H, t, J 8.0 Hz), 8.04 (2H, d, J 8.0 Hz).

Analytical chiral HPLC; 25cm chiral cel OJ-R, flow 0.5ml/min, wavelength 215nm, 50% acetonitrile/$H_3PO_4$-$KH_2PO_4$ [0.2M] pH2, $R_t$ 27.25min.

**Example 18**

**{2-Methyl-4-[((1R)-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)thio]phenoxy}acetic acid**



Prepared from intermediate 37 (29 mg, 0.06 mmol) according to the procedure used for the preparation of example 17 to give the title compound (28 mg, 100%).

LC/MS: m/z 490.0 $[M+H]^+$ $R_t$ 4.60 min.

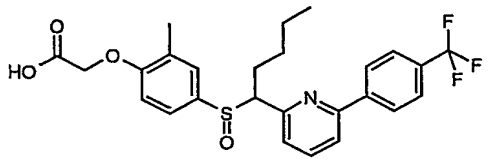
$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.86 (3H, t, 7.0 Hz), 1.23-1.48 (4H, m), 1.95-2.18 (2H, m), 2.08 (3H, s) 4.23 (1H, dd, J 8.5, 6.5 Hz), 4.54 (2H, s), 6.62 (1H, d, J 8.5 Hz), 6.97 (1H, d, J 1.5

Hz), 7.04 (1H, dd, J 8.5 Hz, 1.5 Hz), 7.26 (1H, d, J 8.0 Hz), 7.70 (1H, d, J 8.0 Hz), 7.73 (2H, d, J 8.0 Hz), 7.77 (1H, t, J 8.0 Hz), 8.04 (2H, d, J 8.0 Hz).

Analytical chiral HPLC; 25cm chiral cel OJ-R, flow 0.5ml/min, wavelength 215nm, 50% acetonitrile/$H_3PO_4$-$KH_2PO_4$ [0.2M] pH2, $R_t$ 30.34min.

**Example 19**

**{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)sulfinyl]phenoxy}acetic acid**



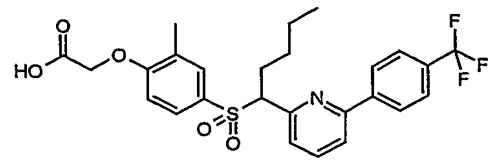
A stirred solution of intermediate 38 (27 mg, 0.05 mmol) in THF (1 mL) and methanol (1 mL) was added, drop-wise, aqueous NaOH (2M, 1 mL). After 2 hours 50 minutes the mixture was concentrated producing a 'chalk-white' solid which was diluted with water (2 mL) and acidified with aqueous HCl (2M, 2 mL). The aqueous layer was extracted with DCM (2 x 2 mL then 1 mL) using a hydrophobic frit and the combined organic layer concentrated under vacuum yielding the title compound as a mixture of two diastereoisomers (24 mg, 94%).

LC/MS: m/z 506.2 $[M+H]^+$, $R_t$ 4.24 min.

$^1$H NMR (400MHz; $CDCl_3$) δ: isomer 1 (70%) 0.83 (3H, t, J 7.0 Hz), 1.17-1.41 (4H, m), 2.06 (3H, s), 1.97-2.42 (2H, m), 4.07 (1H, dd, J 11.0, 4.0 Hz), 4.48 (1H, d, J 17.0 Hz), 4.53 (1H, d, J 17.0 Hz), 6.49 (1H, d, J 8.5 Hz), 6.86 (1H, d, J 2.0 Hz), 6.90 (1H, m), 7.11 (1H, dd, J 8.5, 2.0 Hz), 7.59-7.80 (4H, m), 7.94 (2H, d, 8.0 Hz); isomer 2 (30%) 0.83 (3H, t, J 7.0 Hz), 1.17-1.41 (4H, m), 2.16 (3H, s), 1.97-2.42 (2H, m), 4.14 (1H, m), 4.44 (1H, d, J 17.0 Hz), 4.53 (1H, d, J 17.0 Hz), 6.51 (1H, d, J 8.5 Hz), 7.03 (1H, d, J 2.0 Hz), 7.13 (1H, dd, J 8.5, 2.0 Hz), 7.32 (1H, d, J 8.0 Hz), 7.59-7.80 (6H, m).

**Example 20**

**{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)sulfonyl]phenoxy}acetic acid**



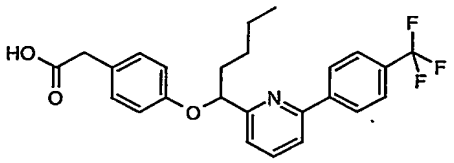
Prepared from intermediate 39 (26 mg, 0.05 mmol) according to the procedure used for the preparation of example 19 to give the title compound as a clear oil (22 mg, 89%).

LC/MS: m/z 522.2 $[M+H]^+$, $R_t$ 4.23 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 0.82 (3H, t, 7.0 Hz), 1.12-1.44 (4H, m), 2.11 (3H, s), 2.26-2.47 (2H,m), 4.40 (1H, dd, 11.5, 4.0 Hz), 4.57 (2H, s), 6.56 (1H, d, 8.5 Hz), 7.27 (1H, m), 7.34 (1H, dd, J 8.5 Hz, 2.0 Hz), 7.47 (1H, d, 7.0 Hz), 7.62 (2H, d, J 8.0 Hz), 7.67 (1H, d, 7.0 Hz), 7.73 (2H, d, J 8.0 Hz), 7.81 (1H, dd, J 7.0, 7.0 Hz).

**Example 21**

**{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}acetic acid**



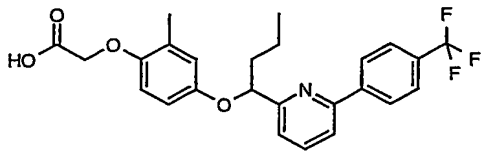
A solution of intermediate 40 (329 mg, 0.72 mmol) in THF (9.5 mL) and methanol (9.5 mL) was treated with aqueous NaOH (2M, 9.5 mL) drop-wise and the resulting solution stirred at rt for 17 hours. The volatile solvents were then removed under vacuum and the resulting aqueous mixture acidified with aqueous HCl (2M, 15 mL), diluted with water (100 mL) and the product extracted with DCM (2 x 100 mL). The combined organic layers were then washed with brine (100 mL), dried ($MgSO_4$), filtered and then reduced under vacuum to give the title compound as a pale yellow foam (314 mg, 98%).

LC/MS: m/z 443.9 $[M+H]^+$, $R_t$ 4.15 min.

$^1H$ NMR (400MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.63 (4H, m), 2.01 (2H, m), 3.52 (2H, s), 5.28 (1H, t, J 6.5 Hz), 6.84 (2H, d, J 9.0 Hz), 7.09 (2H, d, J 9.0 Hz), 7.36 (1H, d, J 7.5 Hz), 7.62 (1H, d, J 8.0 Hz), 7.72 (1H, dd, J 8.0, 7.5 Hz), 7.74 (2H, d, J 8.0 Hz), 8.14 (2H, d, J 8.0 Hz).

**Example 22**

**[2-Methyl-4-(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}butoxy)phenoxy]acetic acid**



A stirred solution of intermediate 42 (50 mg, 0.12 mmol) in DME (0.5 mL) was treated with phenyl 4-(triflouromethyl)benzeneboronic acid (23 mg, 0.12 mmol) followed by $Pd(PPh_3)_4$ (14 mg, 0.01 mmol) and a solution of $Na_2CO_3$ (38 mg, 0.36 mmol) in water (0.5 mL), and the resulting mixture was heated at 70°C for 18 hours under nitrogen. The solvent was then removed under

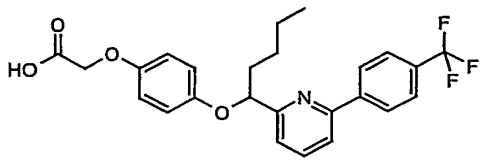
vacuum and the resulting mixture acidified with aqueous HCl (2M) and then partitioned between water and EtOAc, the layers separated and the organic layer reduced to an oil. Purification by mass directed auto-prep HPLC afforded the title compound (12 mg, 23%).

LC/MS: m/z 459.9 $[M+H]^+$, $R_t$ 4.30 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.97 (3H, t, J 7.5 Hz), 1.56 (2H, m), 1.97 (2H, m), 2.19 (3H, s), 4.53 (2H, s), 5.23 (1H, dd, J 6.5, 6.5 Hz), 6.55 (1H, d, J 9.0 Hz), 6.59 (1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, 3.0 Hz), 7.37 (1H, d, 7.5 Hz), 7.61 (1H, d, 7.5 Hz), 7.72 (3H, m), 8.13 (2H, d, 8.5 Hz).

**Example 23**

**{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid**



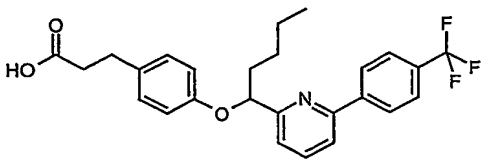
Prepared from intermediate 43 (42 mg, 0.09 mmol) according to the procedure used for the preparation of example 21 to give the title compound as a gum (40 mg, 100%).

LC/MS: m/z 459.9 $[M+H]^+$, $R_t$ 4.31 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.92 (3H, t, J 7.5 Hz), 1.34-1.60 (4H, m), 2.00 (2H, m), 4.51 (2H, s), 5.25 (1H, dd, J 7.5, 5.5 Hz), 6.77 (2H, m), 6.82 (2H, m), 7.41 (1H, dd, J 7.5, 1.5 Hz), 7.78 (2H, d, J 8.0Hz), 7.78-7.86 (2H, m), 8.13 (2H, d, J 8.0 Hz).

**Example 24**

**3-{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}propanoic acid**



To a stirred solution of intermediate 44 (92 mg, 0.19 mmol) in THF (3 mL) and methanol (3 mL) was added, drop-wise, aqueous NaOH (2M, 3 mL). After 17 hours the mixture was concentrated under vacuum and the solid residue acidified with aqueous HCl (2M, 3.5 mL), diluted with water (10 mL) and extracted with DCM (2 x 10 mL). The combined organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under vacuum. The acid was loaded onto a PE-AX isolute SPE cartridge (pre-conditioned with 1 column volume of methanol) in 9 mL of methanol and a few drops of $Et_3N$. The cartridge was washed with 3 column volumes of

methanol followed by 10% aqueous HCl (2M) in methanol (2 x 5 mL) and 20% aqueous HCl (2M) in methanol (2 x 5 mL), yielding the title compound (38 mg, 44%).

LC/MS: m/z 458.0 $[M+H]^+$, $R_t$ 4.11 min.

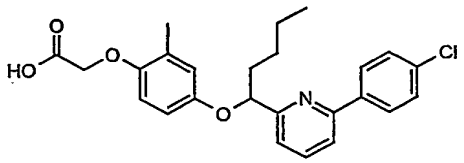
$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.90 (3H, t, 7.0 Hz), 1.32-1.59 (4H, m), 1.94-2.05 (2H, m), 2.47 (2H, t, 7.5 Hz), 2.76 (2H, t, 7.5 Hz), 5.29 (1H, dd, 6.5, 5.5 Hz), 6.78 (2H, d, 8.5 Hz), 7.01 (2H, d, 8.5 Hz), 7.39 (1H, d, 7.5 Hz), 7.78 (4H, m), 8.21 (2H, d, J 8.0 Hz).

**General procedure for the preparation of Examples 25-34**

A stirred solution of intermediate 46 (50 mg, 0.12 mmol) in DME (0.5 mL) was treated with the appropriate aryl boronic acid (0.12 mmol) followed by $Pd(PPh_3)_4$ (13 mg, 0.01 mmol) and a solution of $Na_2CO_3$ (37 mg, 0.34 mmol) in water (0.25 mL). The reaction mixture was heated at 70°C for 18 hours under nitrogen, allowed to cool to rt and then reduced under vacuum (Genevac). The residue was loaded in the minimum volume of methanol onto a SPE (C18 cartridge) (pre-conditioned with 1 column volume of methanol and then 1 column volume of 5% MeCN in water) eluting with 5% MeCN in water, then MeCN followed by methanol to give the crude product. Further purification by mass directed auto-prep HPLC afforded the title compounds.

**Example 25**

**[4-({1-[6-(4-Chlorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

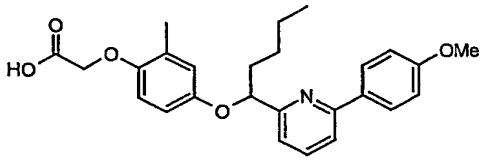


LC/MS: m/z 437.9 $[M-H]^+$, $R_t$ 4.45 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.5 Hz), 1.32-1.61 (4H, m), 1.90-2.05 (2H, m), 2.19 (3H, s), 4.53 (2H, s), 5.21 (1H, dd, J 7.5, 5.5 Hz), 6.54 (1H, d, J 9.0 Hz), 6.58 (1H, dd, J 9.0, 3.0 Hz), 6.77 (1H, d, J 3.0 Hz), 7.32 (1H, d, J 8.0 Hz), 7.44 (2H, d, J 8.5 Hz), 7.54 (1H, d, J 8.0 Hz), 7.68 (1H, t, J 8.0 Hz), 7.95 (2H, d, J 8.5 Hz).

**Example 26**

**[4-({1-[6-(4-Methoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

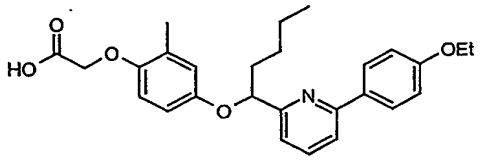


LC/MS: m/z 436.0 $[M+H]^+$, $R_t$ 4.18 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.5 Hz), 1.31-1.62 (4H, m), 1.90-2.06 (2H, m), 2.19 (3H, s), 3.87 (3H, s), 4.53 (2H, s), 5.21 (1H, dd, J 8.0, 5.0 Hz), 6.55 (1H, d, J 9.0 Hz), 6.60 (1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, J 3.0 Hz), 7.01 (2H, d, J 9.0 Hz), 7.26 (1H, d, J 7.5 Hz), 7.51 (1H, d, J 7.5 Hz), 7.66 (1H, t, J 7.5 Hz), 7.95 (2H, d, J 9.0 Hz).

**Example 27**

**[4-({1-[6-(4-Ethoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

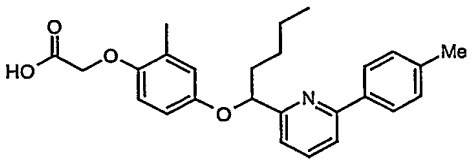


LC/MS: m/z 449.9 $[M+H]^+$, $R_t$ 4.32 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.5 Hz) 1.32-1.62 (4H, m), 1.45 (3H, t, J 7.0 Hz), 1.90-2.05 (2H, m), 2.17 (3H, s), 4.10 (2H, q, J 7.0 Hz), 4.50 (2H, s), 5.19 (1H, dd, J 8.0, 5.0 Hz), 6.54 (1H, d, J 9.0 Hz), 6.58 (1H, dd J 9.0, 3.0), 6.77 (1H, d, J 3.0), 6.99 (2H, d, J 9.0 Hz), 7.23 (1H, d, J 7.5 Hz), 7.49 (1H, d, J 7.5 Hz), 7.63 (1H, t, J 7.5 Hz), 7.94 (2H, d, J 9.0 Hz).

**Example 28**

**[2-Methyl-4-({1-[6-(4-methylphenyl)pyridin-2-yl]pentyl}oxy)phenoxy]acetic acid**



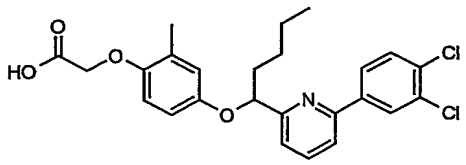
LC/MS: m/z 419.9 $[M+H]^+$, $R_t$ 4.34 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, 7.0 Hz), 1.32-1.61 (4H, m), 1.90-2.06 (2H, m), 2.19 (3H, s), 2.41 (3H, s), 4.52 (2H, s), 5.21 (1H, dd, J 8.0, 5.0 Hz), 6.54 (1H, d, J 9.0 Hz), 6.59

(1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, J 3.0 Hz), 7.27 (1H, dd, J 8.0, 1.0 Hz), 7.28 (2H, d, J 8.0 Hz), 7.53 (1H, dd, J 8.0, 1.0 Hz), 7.65 (1H, t, J 8.0 Hz), 7.89 (2H, d, J 8.0 Hz).

**Example 29**

**[4-({1-[6-(3,4-Dichlorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

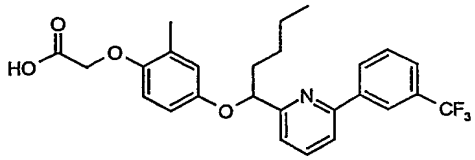


LC/MS: m/z 473.8 $[M+H]^+$, $R_t$ 4.82 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.33-1.61 (4H, m), 1.98 (2H, m), 2.20 (3H, s), 4.54 (2H, s), 5.20 (1H, dd, J 6.5, 6.5 Hz), 6.55 (1H, d, J 9.0 Hz), 6.58 (1H, d, J 9.0, 2.5 Hz), 6.77 (1H, d, J 2.5 Hz), 7.34 (1H, d, J 8.0 Hz), 7.54 (2H, d, J 8.5 Hz), 7.69 (1H, t, J 8.0 Hz), 7.83 (1H, dd, J 8.5, 2.0 Hz), 8.14 (1H, d, J 2.0 Hz).

**Example 30**

**{2-Methyl-4-[(1-{6-[3-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid**

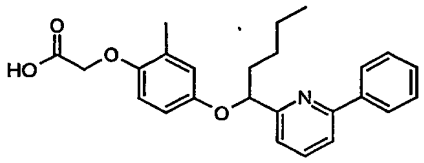


LC/MS: m/z 473.9 $[M+H]^+$, $R_t$ 4.50 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.34-1.62 (4H, m), 1.96-2.04 (2H, m), 2.19 (3H, s), 4.54 (2H, s), 5.22 (1H, m), 6.55 (1H, d, J 9.0 Hz), 6.60 (1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, J 3.0 Hz), 7.36 (1H, d, J 7.5 Hz), 7.60 (1H, m), 7.61 (1H, d, J 8.0 Hz), 7.67 (1H, d, 8.0 Hz) 7.72 (1H, t, J 8.0 Hz), 8.20 (1H, d, J 8.0 Hz), 8.28 (1H, s).

**Example 31**

**(2-Methyl-4-{[1-(6-phenylpyridin-2-yl)pentyl]oxy}phenoxy)acetic acid**

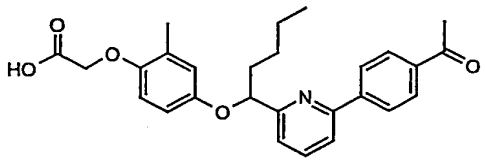


LC/MS: m/z 406.0 $[M+H]^+$, $R_t$ 4.20 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.62 (4H, m), 1.92-2.06 (2H, m), 2.18 (3H, s), 4.49 (2H, s), 5.21 (1H, dd, J 7.5, 5.0 Hz), 6.53 (1H, d, J 9.0 Hz), 6.59 (1H, dd, J 9.0, 3.0 Hz), 6.77 (1H, d, 3.0 Hz), 7.30 (1H, d, 8.0 Hz), 7.41 (1H, m), 7.48 (2H, m), 7.56 (1H, dd, J 8.0, 1.0 Hz), 7.67 (1H, t, J 8.0 Hz), 8.00 (2H, m).

**Example 32**

**[4-({1-[6-(4-Acetylphenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

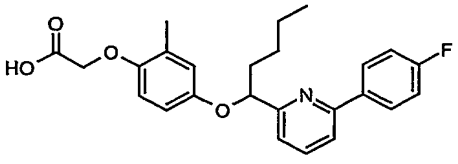


LC/MS: m/z 448.1$[M+H]^+$, $R_t$ 3.93 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.63 (4H, m), 2.00 (2H, m), 2.19 (3H, s), 2.66 (3H, s), 4.53 (2H, s), 5.22 (1H, m), 6.55 (1H, d, J 9.0 Hz), 6.60 (1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, J 3.0 Hz), 7.36 (1H, dd, J 7.5, 1.0 Hz), 7.63 (1H, dd, J 7.5, 1.0 Hz), 7.72 (1H, t, J 7.5 Hz), 8.07 (2H, d, J 8.5 Hz), 8.12 (2H, d, J 8.5 Hz).

**Example 33**

**[4-({1-[6-(4-Fluorophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

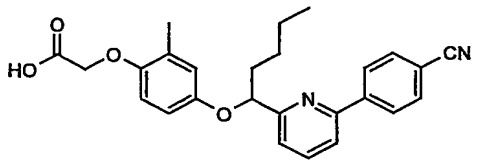


LC/MS: m/z 424.1 $[M+H]^+$, $R_t$ 4.16 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, J 7.0 Hz), 1.32-1.61 (4H, m), 1.99 (2H, m), 2.18 (3H, s), 4.51 (2H, s), 5.19 (1H, dd, J 7.5, 5.5 Hz), 6.53 (1H, d, J 9.0 Hz), 6.58 (1H, dd, J 9.0, 3.0 Hz), 6.77 (1H, d, J 3.0 Hz), 7.16 (2H, m), 7.30 (1H, d, J 7.5 Hz), 7.52 (1H, d, J 7.5 Hz), 7.67 (1H, t, J 7.5 Hz), 7.98 (2H, m).

**Example 34**

**[4-({1-[6-(4-Cyanophenyl)pyridin-2-yl]pentyl}oxy)-2-methylphenoxy]acetic acid**

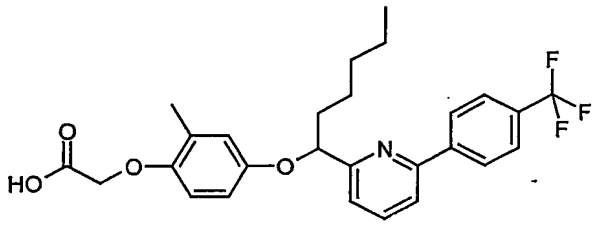


LC/MS: m/z 431.1 $[M+H]^+$, $R_t$ 4.02 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.91 (3H, t, 7.0 Hz), 1.32-1.61 (4H, m), 1.99 (2H, m), 2.19 (3H, s), 4.53 (2H, s), 5.21 (1H, dd, J 6.5, 6.5 Hz), 6.54 (1H, d, J 9.0 Hz), 6.58 (1H, dd, J 9.0, 2.5 Hz), 6.77 (1H, d, J 2.5 Hz), 7.39 (1H, d, J 7.0 Hz), 7.62 (1H, d, J 8.0 Hz), 7.74 (1H, m), 7.77 (2H, d, J 8.5 Hz), 8.14 (2H, dd, J 8.5 Hz).

**Example 35**

**{2-Methyl-4-[(1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}hexyl)oxy]phenoxy}acetic acid**



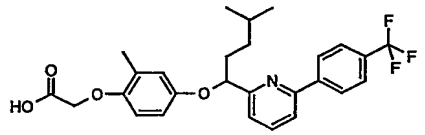
To a solution of intermediate 48 (80 mg, 0.16 mmol) in MeOH (2 mL) and THF (2 mL) at rt was added aqueous NaOH (2M, 1 mL, 2.0 mmol) and the resulting mixture stirred for 2.5 hours. The solvents were then removed under vacuum and the residue partitioned between DCM (20 mL) and aqueous HCl (2M, 20 mL), the layers separated and the aqueous re-extracted with DCM (20 mL). The combined organic solution was passed through a hydrophobic frit and then reduced affording the title compound as colourless oil (57 mg, 75%).

LC/MS: m/z 488.3 $[M+H]^+$, $R_t$ 4.54 min.

$^1H$ NMR (400 MHz; $CDCl_3$) δ: 0.88 (3H, t, J 7.0 Hz), 1.27-1.40 (4H, m), 1.41-1.64 (2H, m), 1.99 (2H, m), 2.20 (3H, s), 4.55 (2H, s), 5.25 (1H, dd, J 6.5, 6.5 Hz), 6.56 (1H, d, J 9.0 Hz), 6.60 (1H, dd, J 9.0 Hz, 3.0 Hz), 6.78 (1H, d, J 3 Hz), 7.38 (1H, d, J 7.5 Hz), 7.62 (1H, d, J 7.5 Hz), 7.74 (1H, t, J 7.5 Hz), 7.74 (2H, d, J 8.0 Hz), 8.13 (2H, d, J 8.0 Hz).

**Example 36**

**{2-Methyl-4-[(4-methyl-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenoxy}acetic acid**



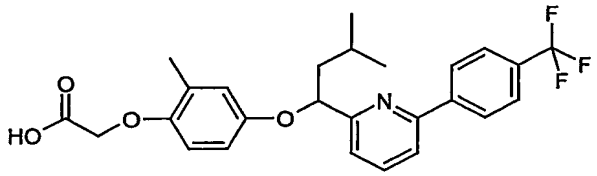
Prepared from intermediate 50 (15 mg, 0.03 mmol) according to the procedure used for the preparation of example 35 to give the title compound as a colourless oil (10 mg, 71%).

LC/MS: m/z 488.1 $[M+H]^+$, $R_t$ 4.49 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.89 (3H, d, J 6.5 Hz), 0.90 (3H, d, J 6.5 Hz), 1.31-1.42 (1H, m), 1.43-1.54 (1H, m), 1.55-1.56 (1H, m), 2.00 (2H, m), 2.20 (3H, s), 4.55 (2H, s), 5.26 (1H, m), 6.56 (1H,d, J 9.0 Hz), 6.61 (1H,.dd, J 9.0, 3.0 Hz), 6.79 (1H, d, J 3.0 Hz), 7.40 (1H, d, J 7.5 Hz), 7.63 (1H, d, J 7.5 Hz), 7.75 (2H, d, J 8.5 Hz), 7.76 (1H,m), 8.13 (2H, d, J 8.5 Hz).

**Example 37**

**[2-Methyl-4-(3-methyl-1-{6-[4-(trifluoromethyl)phenyl]pyridin-2-yl}butoxy)phenoxy]acetic acid**



Prepared from intermediate 52 (132 mg, 0.26 mmol) according to the procedure used for the preparation of example 35 to give the title compound as a pale orange solid (124 mg, 100%).

LC/MS: m/z 474.1 $[M+H]^+$, $R_t$ 4.25 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 1.03 (6H, m), 1.71-2.05 (3H, m), 2.20 (3H, s), 4.55 (2H, s), 5.57 (1H, m), 6.57 (1H, d, J 9.0 Hz), 6.66 (1H, dd, J 8.5 Hz, 3.0 Hz), 6.81 (1H, d, J 3.0 Hz), 7.47 (1H, d, J 8.0 Hz), 7.66 (1H, d, J 8.0 Hz), 7.77 (2H, d, J 8.0 Hz), 7.83 (1H, t, J 8.0 Hz), 8.16 (2H, d, J 8.0 Hz).

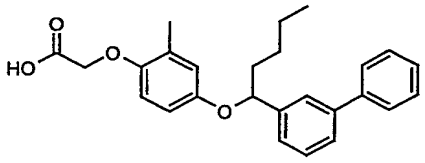
**General procedure for Examples 38 - 40**

A stirred solution of intermediate 22 (50 mg, 0.11 mmol) in DME (0.5 mL) was treated with the appropriate aryl boronic acid (0.11 mmol) followed by $Pd(PPh_3)_4$ (13 mg, 0.01 mmol) and a solution of $Na_2CO_3$ (37 mg, 0.33 mmol) in water (0.25 mL). The reaction mixture was heated at 70°C for 18 hours under nitrogen, allowed to cool to rt and then reduced under vacuum

(Genevac). The residue was loaded in the minimum volume of methanol onto a SPE (C18 cartridges) (pre-conditioned with 1 column volume of methanol and then 1 column volume of 5% MeCN in water) eluting with 5% MeCN in water, then MeCN followed by methanol to give the crude product. Further purification by mass directed auto-prep HPLC afforded the title compounds.

**Example 38**

**(4-{[1-(1,1'-Biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid**

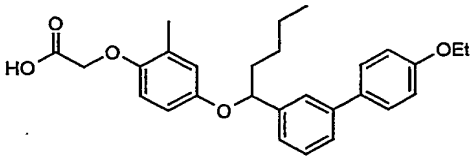


LC/MS: m/z 422.1 $[M+H]^+$, $R_t$ 4.24 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.89 (3H, t, J 7.0 Hz), 1.29-1.42 (3H, m), 1.44-1.57 (1H, m), 1.75-1.87 (1H, m), 1.93-2.05 (1H, m), 2.09 (3H, s), 4.35 (2H, s), 4.99 (1H, dd, J 8.0, 5.0 Hz), 6.46 (1H, d, J 9.0 Hz), 6.53 (1H, d, 9.0, 3.0 Hz), 6.69 (1H, d, 3.0 Hz), 7.24-7.46 (6H, m), 7.51-7.58 (3H, m).

**Example 39**

**(4-{[1-(4'-Ethoxy-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid**

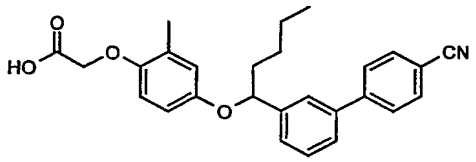


LC/MS: m/z 466.1 $[M+NH_4]^+$, $R_t$ 4.29 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.89 (3H, t, J 7.0 Hz), 1.35 (3H, m), 1.42 (3H, t, J 7.0 Hz), 1.46-1.58 (1H, m), 1.75-1.86 (1H, m), 1.92-2.03 (1H, m), 2.10 (3H, s), 4.05 (2H, q, J 7.0 Hz), 4.38 (2H, s), 4.98 (1H, dd, J 8.0, 5.5 Hz), 6.47 (1H, d, J 9.0 Hz), 6.54 (1H, dd, J 9.0, 2.5 Hz), 6.70 (1H, d, J 2.5 Hz), 6.93 (2H, d, J 9.0 Hz), 7.23 (1H, d, J 7.5 Hz); 7.32 (1H, t, J 7.5 Hz), 7.40 (1H, d, J 7.5 Hz), 7.47 (2H, d, J 9.0 Hz), 7.49 (1H, m).

**Example 40**

**(4-{[1-(4'-Cyano-1,1'-biphenyl-3-yl)pentyl]oxy}-2-methylphenoxy)acetic acid**



LC/MS: m/z 447.3 $[M+NH_4]^+$, $R_t$ 4.20 min.

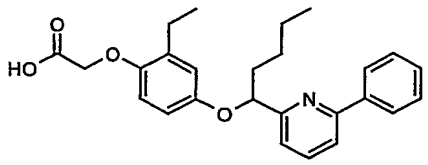
$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, 7.0 Hz), 1.36 (3H, m), 1.45-1.57 (1H, m), 1.81 (1H, m), 1.98 (1H, m), 2.11 (3H, s), 4.39 (2H, s), 5.02 (1H, dd, J 8.0, 5.0 Hz), 6.48 (1H, d, J 9.0 Hz), 6.52 (1H, dd, J 9.0, 2.5 Hz), 6.70 (1H, d, J 2.5 Hz), 7.34-7.47 (3H, m), 7.53 (1H, s), 7.62 (2H, d, J 8.0 Hz), 7.68 (2H, d, J 8.0 Hz).

**General procedure for Examples 41-44**

A stirred solution of intermediate 53 (50 mg, 0.11 mmol) in DME (0.5 mL) was treated with the appropriate aryl boronic acid (0.11 mmol) followed by $Pd(PPh_3)_4$ (13 mg, 0.01 mmol) and a solution of $Na_2CO_3$ (37 mg, 0.33 mmol) in water (0.25 mL). The reaction mixture was heated at 70°C for 18 hours under nitrogen, allowed to cool to rt and then reduced under vacuum (Genevac). The residue was loaded in the minimum volume of methanol onto a SPE (C18 cartridges) (pre-conditioned with 1 column volume of methanol and then 1 column volume of 5% MeCN in water) eluting with 5% MeCN in water, then MeCN followed by methanol to give the crude product. Further purification by mass directed auto-prep HPLC afforded the title compounds.

**Example 41**

**(2-Ethyl-4-{[1-(6-phenylpyridin-2-yl)pentyl]oxy}phenoxy)acetic acid**

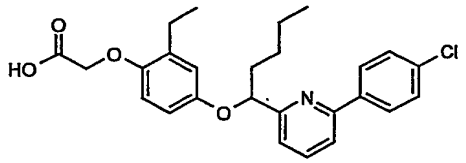


LC/MS: m/z 420.2 $[M+H]^+$, $R_t$ 4.33 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.5 Hz), 1.07 (3H, t, J 7.5 Hz), 1.32-1.62 (4H, m), 1.99 (2H, m), 2.51 (2H, q, J 7.5 Hz), 4.37 (2H, s), 5.21 (1H, m), 6.48 (1H, d, J 9.0 Hz), 6.55 (1H, d, J 9.0 Hz), 6.76 (1H, dd, J 9.0, 3.0 Hz), 7.28 (1H, d, J 7.5 Hz), 7.40 (1H, m), 7.46 (2H, m), 7.53 (1H, d, J 7.5 Hz), 7.62 (1H, t, J 7.5 Hz), 7.99 (2H, m).

**Example 42**

**[4-({1-[6-(4-Chlorophenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid**

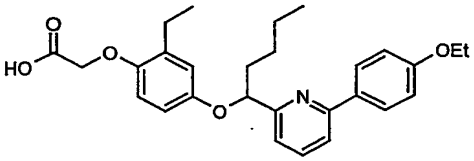


LC/MS: m/z 454.1 $[M+H]^+$, $R_t$ 4.55 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.5 Hz), 1.10 (3H, t, J 7.5 Hz), 1.32-1.61 (4H, m), 1.99 (2H, m), 2.55 (2H, q, J 7.5 Hz), 4.45 (2H, s), 5.20 (1H, dd, J 6.5, 6.5 Hz), 6.51 (1H, d, J 9.0 Hz), 6.56 (1H, dd, J 9.0, 3.0 Hz), 6.78 (1H, d, J 3.0 Hz), 7.30 (1H, d, J 7.5 Hz), 7.44 (2H, d, J 8.5 Hz), 7.52 (1H, d, J 7.5 Hz), 7.65 (1H, t, J 7.5 Hz), 7.95 (2H, d, J 8.5 Hz).

**Example 43**

**[4-({1-[6-(4-Ethoxyphenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid**

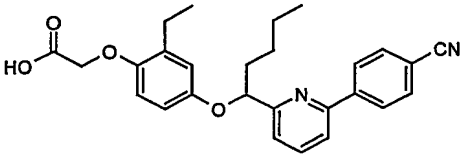


LC/MS: m/z 464.2 $[M+H]^+$, $R_t$ 4.39 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.0 Hz), 1.08 (3H, t, J 7.5 Hz), 1.44 (3H, t, J 7.0 Hz), 1.32-1.61 (4H, m), 1.98 (2H, m), 2.53 (2H, q, J 7.5 Hz), 4.09 (2H, q, J 7.0 Hz), 4.41 (2H, s), 5.19 (1H, dd, J 7.5, 5.0 Hz), 6.49 (1H, d, J 9.0 Hz), 6.56 (1H, dd, J 9.0, 3.0 Hz), 6.77 (1H, d, J 3.0 Hz), 6.98 (2H, d, J 9.0 Hz), 7.22 (1H, d J 7.5 Hz), 7.47 (1H, d, J 7.5 Hz), 7.59 (1H, t, J 7.5 Hz), 7.94 (2H, d, J 9.0 Hz).

**Example 44**

**[4-({1-[6-(4-Cyanophenyl)pyridin-2-yl]pentyl}oxy)-2-ethylphenoxy]acetic acid**



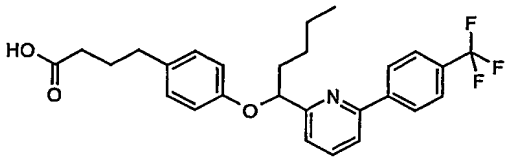
LC/MS: m/z 445.0 $[M+H]^+$, $R_t$ 4.09 min.

$^1$H NMR (400 MHz; $CDCl_3$) δ: 0.90 (3H, t, J 7.0 Hz), 1.09 (3H, t, J 7.5 Hz), 1.32-1.62 (4H, m), 1.99 (2H, m), 2.54 (2H, q, J 7.5 Hz), 4.43 (2H, s), 5.21 (1H, dd, J 6.0 Hz), 6.50 (1H, d, J 9.0

Hz), 6.54 (1H, dd, J 9.0, 2.5 Hz), 6.77 (1H, d, J 2.5 Hz), 7.38 (1H, d, J 8.0 Hz), 7.60 (1H, d, J 8.0 Hz), 7.71 (1H, t, J 8.0 Hz), 7.70 (2H, d, J 8.5 Hz), 8.13 (2H, d, J 8.5 Hz).

**Example 45**

**4-{4-[(1-{6-[4-(Trifluoromethyl)phenyl]pyridin-2-yl}pentyl)oxy]phenyl}butanoic acid**



To a stirred solution of intermediate 55 (42 mg, 0.07 mmol) in THF at rt was added, dropwise, TBAF (70 µL of a 1.0M solution in THF, 0.07 mmol) and the mixture stirred at rt for 1.5 hours. Additional TBAF (35 µL of a 1.0M solution in THF, 0.04 mmol) was then added and the mixture left to stir at rt for17.5 hours. The mixture was then concentrated under vacuum and the residue purified by SPE (silica, 1 g Cartridge) eluting with cyclohexane : EtOAc (gradient 25:1 to 0:1), then EtOAc : MeOH (gradient 10:1 to 0:1) to give a crude product which was purified further by mass directed auto-prep HPLC to give the title compound (6.4 mg, 19%).

LC/MS: m/z 472.15 $[M+H]^+$, $R_t$ 4.21 min.

$^1$H NMR (400MHz; MeOD-$d^4$) δ: 0.92 (3H, t, 7.0 Hz), 1.34-1.61 (4H, m), 1.80 (2H, m), 2.00 (2H, m), 2.22 (2H, t, 7.5 Hz), 2.51 (2H, t, 7.5 Hz), 5.29 (1H, dd, 7.0, 6.0 Hz), 6.79 (2H, d, 9.0 Hz), 7.00 (2H, d, 9.0 Hz), 7.40 (1H, dd, J 7.0, 1.5 Hz), 7.75-7.85 (4H, m), 8.23 (2H, d, J 8.5 Hz).

The following intermediates and ligands were prepared for the binding and transfection assays described below:

(i) 2-{2-methyl-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid.

This compound was used as a PPARdelta reference in the transfection assays described below and was prepared according to the method reported in WO200100603-A1

(ii) 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-yl carbonyl)amino]methyl}-phenoxy]propionic acid.

This compound was used as a PPAR alpha reference in the transfection assay described below and was prepared according to method reported in WO200140207-A1

(iii) 5-{4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4 -dione

This compound was used as a PPAR gamma reference in the transfection assay described below and was prepared according to method reported in *J.Med.Chem.* 1994, *37(23)*, 3977

**Binding Assay:**

Compounds were tested for their ability to bind to hPPAR gamma hPPARalpha or hPPARdelta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBD) was expressed in E. coli as polyHis tagged fusion proteins and purified. The LBD was then labelled with biotin and immobilised on streptavidin-modified scintillation proximity beads. The beads were then incubated with a constant amount of the appropriate radioligand (3H-BRL 49653 for PPARgamma, and labelled GW 2433 (see Brown, P. J et al . *Chem. Biol.*, 4, 909-918 (1997). for the structure and synthesis of this ligand) for PPARalpha and PPAR delta and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads was measured by a scintillation counter. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound were constructed and apparent Ki values were estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain. *Anal. Biochem.*, 257, 112-119 (1998)).

**Transfection assay:**

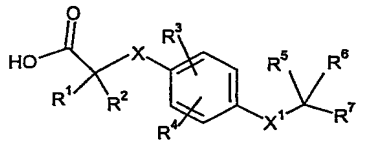
Compounds were screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPARgamma), *J. Biol. Chem.*, 270, 12953-6 (1995). The ligand binding domains for murine and human PPAR alpha, PPAR gamma, and PPAR delta were each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and beta-galactosidase. After 16 h, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24h, cell extracts were prepared and assayed for alkaline phosphatase and beta-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the beta-galactosidase activity as an internal standard (see, for example, Kliewer, S. A., et. al. Cell 83, 813-819 (1995)). Rosiglitazone (BRL 49653) was used as a positive control in the hPPAR gamma assay. The positive control in the hPPAR alpha assays was 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-yl-carbonyl)amino]methyl}-phenoxy]propionic acid. The positive control for PPAR delta assays was 2-{2-methyl-4-[({4-methyl-2-{trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid.

All of the above acid Examples showed at least 50% activation of PPARd relative to the positive control at concentrations of $10^{-7}$ M or less

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein. This may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims.

What is claimed is:

1. A compound of formula (I) or a pharmaceutically acceptable salt, solvate, or hydrolysable ester thereof, wherein:



(1)

wherein:

$R^1$ and $R^2$ are independently H or $C_{1-3}$ alkyl;

X represents a O or $(CH_2)_n$ where n is 0, 1 or 2;

$R^3$and $R^4$ independently represent H, $C_{1-3}$ alkyl, $-OCH_3$, $-CF_3$, allyl, or halogen;

$X^1$ represents O, S, $SO_2$, SO, or $CH_2$;

$R^5$ and $R^6$ independently represent hydrogen, $C_{1-6}$ alkyl (including branched alkyl and optionally substituted by one or more halogens or $C_{1-6}$alkoxy), or together with the carbon atom to which they are bonded form a 3-6 membered cycloalkyl ring;

$R^7$ represents a phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1,.2 or 3 moieties selected from the group consisting of halogen, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl, $CF_3$, hydroxy, phenyl (which may be optionally substituted by one or more $C_{1-3}$ alkyl, $-OC_{1-3}$ alkyl, CN, acetyl, hydroxy, halogen or $CF_3$).

2. A compound according to claim 1 for use in therapy.

3. A pharmaceutical composition comprising a compound according to claim 1.

4. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of a hPPAR disease or condition.

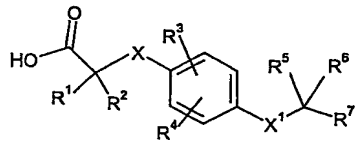
5. Use according to claim 4 wherein the hPPAR mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa

6. A method of treating a hPPAR mediated disease or condition in a patient comprising the administration of a therapeutically effective amount of a compound according to claims 1.

7. A method according to claim 6 wherein the hPPAR mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, anorexia bulimia and anorexia nervosa.

Abstract

The present invention provides a compound of formula (I):



(1)

wherein:

$R^1$ and $R^2$ are independently H or $C_{1-3}$ alkyl;

X represents a O or $(CH_2)_n$ where n is 0, 1 or 2;

$R^3$and $R^4$ independently represent H, $C_{1-3}$ alkyl, $-OCH_3$, $-CF_3$, allyl, or halogen;

$X^1$ represents O, S, $SO_2$, SO, or $CH_2$;

$R^5$ and $R^6$ independently represent hydrogen, $C_{1-6}$ alkyl (including branched alkyl and optionally substituted by one or more halogens or $C_{1-6}$alkoxy), or together with the carbon atom to which they are bonded form a 3-6 membered cycloalkyl ring;

$R^7$ represents a phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1,.2 or 3 moieties selected from the group consisting of halogen, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl, $CF_3$, hydroxy, phenyl (which may be optionally substituted by one or more $C_{1-3}$ alkyl, $-OC_{1-3}$ alkyl, CN, acetyl, hydroxy, halogen or $CF_3$).